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(54) Biphenylderivatives, process for their preparation and their use as medicaments

Biphenylderivate, Verfahren zu ihrer Herstellung und ihre Anwendung als Arzneimittel

Dérivés de biphényle, procédé pour leur préparation et leur utilisation comme médicaments

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(73) Proprietor: **Eisai Co., Ltd.**
Tokyo (JP)

(72) Inventors:
- **Akasaka, Kozo**
  Ushiku-shi, Ibaraki (JP)
- **Yonaga, Masahiro**
  Tsukuba-shi, Ibaraki (JP)
- **Kajiwara, Akiharu**
  London, N12 7JG (GB)
- **Higurashi, Kunizo**
  Abiko-shi, Chiba (JP)
- **Ueno, Kohshi**
  Tsukuba-shi, Ibaraki (JP)
- **Nagato, Satoshi**
  London, NW8 6LD (GB)
- **Komatsu, Makoto**
  Tsukuba-shi, Ibaraki (JP)
- **Kitazawa, Noritaka**
  Tsukuba-shi, Ibaraki (JP)
- **Ueno, Masataka**
  Kitasouma-gun, Ibaraki (JP)
- **Yamanishi, Yoshiharu**
  Ryugasaki-shi, Ibaraki (JP)
- **Machida, Yoshimasa**
  London, NW8 (GB)
- **Komatsu, Yuki**
  Tsukuba-shi, Ibaraki (JP)
- **Shimomura, Naoyuki**
  Tsukuba-shi, Ibaraki (JP)
- **Minami, Norio**
  Tsukuba-shi, Ibaraki (JP)
- **Shimizu, Toshikazu**
  Kashima-gun, Ibaraki (JP)
- **Nagaoka, Atsushi**
  Kashima-gun, Ibaraki (JP)

(74) Representative:
Hansen, Bernd, Dr. Dipl.-Chem. et al
Hoffmann Eitle,
Patent- und Rechtsanwälte,
Arabellastrasse 4
81925 München (DE)

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(56) References cited:

EP-A- 0 100 257	EP-A- 0 256 936
EP-A- 0 385 237	EP-A- 0 574 271
WO-A-92/19624	WO-A-94/24116
GB-A- 2 017 698	US-A- 4 125 612

- **CHEMICAL ABSTRACTS, vol. 70, no. 11, 17 March 1969 Columbus, Ohio, US; abstract no. 47401s, XP002034349 & JOURNAL OF MEDICINAL CHEMISTRY, vol. 12, no. 1, 1969, WASHINGTON US, pages 25-29, W.G. DUNCAN ET AL.: & CAS REGISTRY (STN DATABASE):**
- **CHEMICAL ABSTRACTS, vol. 114, no. 1, 7 January 1991 Columbus, Ohio, US; abstract no. 6439u, XP002034350 & AUST. J. CHEM., vol. 43, no. 8, 1990, pages 1367-1373, G.B. BARLIN ET AL.: & CAS REGISTRY (STN DATABASE):**
- **REGISTRY HANDBOOK 1974 SUPPL.: , CHEM. ABS. SERVICE ACS XP002034348 * RN: 47497-49-4, 47069-47-6 ***

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

Background of the Invention

Field of the Invention

[0001] The present invention relates to biphenyl derivatives. More particularly, it relates to biphenyl derivatives which exhibit dopamine 2 receptor antagonism and/or serotonin 2 receptor antagonism and which are clinically useful as therapeutic and ameliorative agents for mental disorders such as cerebrovascular disorder, aggressive behavior due to senile dementia, mental excitation, poriomania, delirium, hallucination, hyperkinesia, schizophrenia, emotional disturbance, depression, neurosis, psychophysiologic disorder and anxiety neurosis.

Description of the Related Art

[0002] Mental disorders such as cerebrovascular disorder and dementia are frequently found in the aged, which becomes a significant problem with the approach of an aging society. In many cases, these diseases are accompanied with mental and/or behavior disorders which specifically appear as delirium, hallucination, hyperkinesia, poriomania, mental excitation or other sign or symptom. These signs and symptoms not only have an adverse effect on a patient himself, but also necessitate everyday care, imposing a heavy burden on the people around the patient. Under these circumstances, the development of a highly clinically useful medicine which can treat the above mental disorders medically has been expected not only by patients and their families, but also socially.

[0003] Only Tiapride is now authorized as a therapeutic and ameliorative agent for the above diseases, and Haloperidol which is an antischizophrenic drug is also used, though the diseases are not included in the indications for which the drug is efficacious.

[0004] As novel compounds having an antipsychotic activity, benzisothiazole derivatives and benzisoxazole derivatives are disclosed in European Patent Publication-A No. 196132, and pyridine derivatives are disclosed in U. S. Patent No. 5021421.

[0005] Tiapride and Haloperidol are medicines exhibiting dopamine 2 (D_2) receptor antagonism. A medicine of this type has a problem of causing extrapyramidal syndrome including dystonia (hypermyotonia or muscle hypotonia), hypokinesis (akinesis), hyperkinesia (abnormal movement) and so forth as an adverse reaction, though the medicine is clinically efficacious.

[0006] Risperidone which is a representative example of the benzisoxazole derivative disclosed in the above European Patent Publication-A No. 196132 is authorized as an antischizophrenic drug in the United States, the United Kingdom and Canada. However, this drug is problematic in that blood-pressure drop occurs as an adverse reaction owing to the high α_1 blocking activity of the drug and that the QT_C interval in electrocardiogram is lengthened to induce arrhythmia, being undesirable particularly when administered to a patient of advanced age.

[0007] The pyridine derivative disclosed in the above U. S. Patent No. 5021421 also exhibits potent dopamine 2 receptor antagonism and is therefore feared to cause extrapyramidal syndrome like Tiapride or Haloperidol. Further, the pyridine derivative has not been used clinically as yet, so that its safeness in prolonged application is not apparent.

[0008] As described above, there has not been found any therapeutic and ameliorative agent for mental disorders such as cerebrovascular disorder, aggressive behavior due to senile dementia, mental excitation, poriomania, delirium, hallucination, hyperkinesia, schizophrenia, emotional disturbance, depression, neurosis, psychophysiologic disorder and anxiety neurosis, which has high clinical usefulness and is excellent in safeness.

Disclosure of the Invention

Summary of the Invention

[0009] An object of the present invention is to provide novel biphenyl derivatives and pharmacologically acceptable salts thereof which exhibit dopamine 2 receptor antagonism and/or serotonin 2 receptor antagonism, are clinically useful as therapeutic and ameliorative agents for mental diseases, is improved in the disadvantageous extrapyramidal syndrome as compared with dopamine 2 receptor antagonists of the prior art such as Tiapride and Haloperidol, and is freed from the adverse reactions caused by the above benzisoxazole derivative (such as Risperidone), for example, blood-pressure drop and induction of arrhythmia.

[0010] Another object of the present invention is to provide processes for the preparation of the biphenyl derivatives described above.

[0011] Another object of the present invention is to provide phenylpiperazine derivatives and salts thereof which are useful as intermediates in the production of the biphenyl derivatives and pharmacologically acceptable salts thereof

described above.

[0012] The present inventors have extensively studied to find an extremely safe and useful therapeutic and ameliorative agent for mental disorders which exhibits dopamine 2 receptor antagonism and does not cause extrapyramidal syndrome, blood-pressure drop, induction of arrhythmia or other adverse reaction, with their attention being paid to compounds exhibiting both dopamine 2 receptor antagonism and serotonin 2 receptor antagonism. As a result, they have found that specific biphenyl derivatives and pharmacologically acceptable salts thereof which are novel compounds have an excellent therapeutic and ameliorative effect on mental disorders and are excellent in safeness, solving the above problems. The present invention has been accomplished on the basis of this finding.

[0013] Thus, the present invention provides a biphenyl derivative as defined in claim 1. Preferred embodiments of the biphenyl derivative are described in the dependent claims 2 to 5.

[0014] Further, the present invention provides a therapeutic and ameliorative agent for a mental disorder, which comprises a biphenyl derivative or a pharmacologically acceptable salt thereof as set forth in claim 1 as an active ingredient.

[0015] Furthermore, the present invention provides a pharmacological composition which comprises a therapeutically or amelioratively effective amount of a biphenyl derivative or the pharmacologically acceptable salt thereof as set forth in claim 1, and a pharmacologically acceptable vehicle; an use of a biphenyl derivative or the pharmacologically acceptable salt thereof as set forth in claim 1 for the making of a medicament for treating or ameliorating a disease against which dopamine 2 receptor antagonism and/or serotonin 2 receptor antagonism is efficacious.

[0016] In addition, the present invention provides processes for the production of the above-mentioned biphenyl derivatives, which is defined in claim 9. The present invention furthermore provides a phenylpiperazine derivative, which is defined in claim 28.

[0017] Further applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the scope of the invention as defined in the claims will become apparent to those skilled in the art from this detailed description.

Detailed Description of the Invention

[0018] With respect to the definition of the formulas of the claims, particular examples of the halogen atom include chlorine atom, fluorine atom, bromine atom and iodine atom, among which fluorine atom and chlorine atom are preferable. The lower alkyl group is an alkyl group having 1 to 6 carbon atoms, such as methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, i-butyl group, t-butyl group, pentyl group and hexyl group; the halogenated lower alkyl group is a lower alkyl group described above in which at least one halogen atom substitutes for the hydrogen atom, and particular examples thereof include fluoromethyl group, difluoromethyl group, trifluoromethyl group, fluoroethyl group, fluoropropyl group, chlorobutyl group and chloropentyl group; the lower alkoxy group is a lower alkyl group described above to which an oxygen atom is bonded, and particular examples thereof include methoxy group, ethoxy group and propoxy group; the halogenated lower alkoxy group is a lower alkoxy group described above in which at least one halogen atom substitutes for the hydrogen atom, and particular examples thereof include fluoromethoxy group and chloroethoxy group; the lower alkoxyalkyl group is a lower alkyl group described above in which a lower alkoxy group substitutes for the hydrogen atom, and particular examples thereof include methoxymethyl group, methoxyethyl group and methoxypropyl group; the lower alkoxyalkoxy group is a lower alkoxy group described above in which a lower alkoxy group substitutes for the hydrogen atom bonded to the carbon atom, and particular examples thereof include methoxy-methoxy group, methoxyethoxy group and methoxypropoxy group; the aryl group denotes a phenyl group, tolyl group ($-C_6H_4CH_3$), xylyl group [$-C_6H_3(CH_3)_2$], methoxyphenyl group, chlorophenyl group, bromophenyl group, fluorophenyl group, nitrophenyl group and cyanophenyl group; particular examples of the aralkyl group include benzyl group, methylbenzyl group, phenethyl group and phenylpropyl group; the heteroaryl group denotes a thienyl group, furanyl group, pyranyl group, imidazolyl group, thiazolyl group, pyridyl group and pyrazyl group; the heteroarylalkyl group denotes a thienylmethyl group, furfuryl group, imidazolylmethyl group, thiazolylmethyl group, pyridylmethyl group and pyrazylmethyl group; the halogenated heteroarylalkyl group is a heteroarylalkyl group described above in which at least one halogen atom substitutes for the hydrogen atom; the cyano lower alkyl group is a lower alkyl group described above in which at least one cyano group substitutes for the hydrogen atom; the hydroxy lower alkyl group is a lower alkyl group described above in which at least one hydroxyl group substitutes for the hydrogen atom; the amino lower alkyl group is a lower alkyl group described above in which at least one amino group substitutes for the hydrogen atom; the lower alkoxycarbonyl group is a lower alkoxy group described above to which a carbonyl group is bonded, and particular examples thereof include methoxy carbonyl group and ethoxycarbonyl group; the aryloxycarbonyl group is an aryl group described above to which an oxygen atom having a carbonyl group bonded thereto is bonded, and particular examples thereof include phenoxycarbonyl group, tolyloxycarbonyl group and xyly-

loxycarbonyl group; the lower acyl group is a lower alkyl group which has 1 to 6 carbon atoms and to which a carbonyl group is bonded, and particular examples thereof include acetyl group, propionyl group, butyryl group and valeryl group; particular examples of the aromatic acyl group include benzoyl group, anisoyl group, nitrobenzoyl group, chlorobenzoyl group, cyanobenzoyl group, toluoyl group and xyloyl group; particular examples of the cycloether group include tetrahydrofuranyl group and tetrahydropyranyl group; particular examples of the alkenyl group include vinyl group, propenyl group and butenyl group; a particular example of the alkynyl group includes propargyl group; the lower alkylsulfinyl group is a lower alkyl group described above to which a sulfinyl group (-SO-) is bonded, and particular examples thereof include methanesulfinyl group and ethanesulfinyl group; the lower alkylsulfonyl group is a lower alkyl group described above to which a sulfonyl group ($-SO_2-$) is bonded, and particular examples thereof include methanesulfonyl group and ethanesulfonyl group; the lower alkylaminosulfonyl group is an aminosulfonyl group ($>NSO_2-$) in which the N atom has one lower alkyl group described above and one hydrogen atom bonded thereto, or two lower alkyl groups described above bonded thereto, and particular examples thereof include methylaminosulfonyl group and dimethylaminosulfonyl group; the arylaminosulfonyl group is an aminosulfonyl group in which the N atom has one aryl group described above bonded thereto, or two aryl groups described above bonded thereto, and particular examples thereof include phenylaminosulfonyl group and diphenylaminosulfonyl group; the lower alkylsulfonylamino group is a lower alkyl group described above to which a sulfonylamino group ($-SO_2NH-$) is bonded, and particular examples thereof include methanesulfonylamino group, ethanesulfonylamino group, propanesulfonylamino group and butanesulfonylamino group; the halogenated lower alkylsulfonylamino group is a lower alkylsulfonylamino group described above in which at least one halogen atom substitutes for the hydrogen atom; the arylsulfonylamino group is an aryl group described above to which a sulfonylamino group ($-SO_2NH-$) is bonded, and particular examples thereof include benzenesulfonylamino group and toluenesulfonylamino group; the cyclic acetal group is, i.e., an alkyldioxymethyl group, and examples thereof include 1,3-dioxolan-2-yl group and 1,3-dioxan-2-yl group; and the cyclic thioacetal group is, i.e., an alkyldithiomethyl group, and an example thereof includes 1,3-dithian-2-yl group. In particular, it is preferable that R^1 be a halogenated lower alkyl group or a lower alkylsulfonylamino group, R^2 be a halogen atom or a lower alkoxy group, R^3 be a halogen atom, a lower alkyl group or a cyano group, R^4 be a hydrogen atom or a halogen atom, R^5 be a hydrogen atom, a lower alkyl group or a hydroxy lower alkyl group. Further, it is preferable that the substituent represented by formula $-(CH_2)$-piperazine-R^5 be bonded at the 3-position of the 1,1'-biphenyl skeleton, though the position of substitution is not particularly limited.

[0019] More specific examples of the biphenyl derivative represented by the above formula (I) or (II) according to the present invention include the following compounds, though the derivative represented by the above formula (I) or (II) is not limited to them:

(1) 1-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(2) 1-(2-hydroxyethyl)-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(3) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-ethoxycarbonyl]phenylpiperazine,
(4) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-amino]-phenylpiperazine,
(5) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(6) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine.
(7) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-butanesulfonylamino]phenylpiperazine,
(8) 1-methyl-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(9) 1-ethyl-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(10) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(11) 1-(2-hydroxyethyl)-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(12) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(13) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(14) 1-(2-hydroxyethyl)-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(15) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(16) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine,
(17) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(18) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-butanesulfonylamino]phenylpiperazine,
(19) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine,
(20) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(21) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-butanesulfonylaminolphenylpiperazine,
(22) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine,
(23) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(24) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-butanesulfonylamino]phenylpiperazine,
(25) 1-ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonylamino]phenylpiperazine,
(26) 1-ethyl-4-(3-phenyl-4-methoxy-5-chloromethyl)-phenylpiperazine,

(27) 1-ethyl-4-(3-phenyl-4-methoxy-5-[1-fluoro-(4-pentenyl)]]phenylpiperazine,
(28) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-fluorobutyl)]phenylpiperazine,
(29) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-fluoropentyl)]phenylpiperazine,
(30) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine,
(31) 1-ethyl-4-[3-(2-tolyl)-4-fluoro-5-(l-fluorobutyl)]phenylpiperazine,
(32) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoro-3-methylbutyl)]phenylpiperazine,
(33) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(l-fluoroethyl)]phenylpiperazine,
(34) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine,
(35) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine,
(36) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1,1-difluoropropyl)]phenylpiperazine,
(37) 1-ethyl-4-(3,5-diphenyl-4-methoxy)phenylpiperazine,
(38) 1-ethyl-4-(3-phenyl-4-methoxy)phenylpiperazine.
(39) 1-ethyl-4-(3,5-diphenyl-4-hydroxy)phenylpiperazine,
(40) 1-ethyl-4-(3-phenyl-4-methoxy-5-propyl)phenylpiperazine,
(41) 1-ethyl-4-(3,5-diphenyl-4-isopropoxy)phenylpiperazine,
(42) 1-ethyl-4-(3-phenyl-4-isopropoxy)phenylpiperazine,
(43) 1-ethyl-4-(3-phenyl-4-hydroxy)phenylpiperazine,
(44) 1-ethyl-4-[2-methoxy-3-phenyl-5-(3-hydroxypropyl)]phenylpiperazine,
(45) 1-hydroxyethyl-4-(3,5-diphenyl-4-methoxy)phenylpiperazine,
(46) 1-ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-propyl)]phenylpiperazine,
(47) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxyethyl)]phenylpiperazine,
(48) 1-ethyl-4-[2-methoxy-3-phenyl-5-(2-hydroxyethyl)]phenylpiperazine,
(49) 1-ethyl-4-[3-phenyl-4-methoxy-5-(3-methoxypropyl)]phenylpiperazine,
(50) 1-ethyl-4-[3-phenyl-4-methoxy-5-(3-methoxymethoxypropyl)]phenylpiperazine,
(51) 1-ethyl-4-(3-phenyl-4-methoxy-5-ethyl)phenylpiperazine,
(52) 1-ethyl-4-[3-phenyl-4-methoxy-5-(3-cyanopropyl)]phenylpiperazine,
(53) 1-(2-fluoroethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-propyl]phenylpiperazine,
(54) 1-ethyl-4-[3-(4-methoxyphenyl)-4-methoxy-5-propyl]phenylpiperazine,
(55) 1-ethyl-4-(3-phenyl-4-methoxy-5-methoxycarbonyl)phenylpiperazine,
(56) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxypropyl)]phenylpiperazine,
(57) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-fluoroethyl)]phenylpiperazine,
(58) 1-ethyl-4-[3-phenyl-4-methoxy-5-(3-fluoropropyl)]phenylpiperazine,
(59) 1-ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-isopropyl]phenylpiperazine,
(60) 1-ethyl-4-[3-(4-fluorophenyl)-4-methoxy-6-isopropyl]phenylpiperazine,
(61) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxyisopropyl)]phenylpiperazine,
(62) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-butoxypropyl)]phenylpiperazine,
(63) 1-ethyl-4-(3-phenyl-4-methoxy-5-propionyl)-phenylpiperazine,
(64) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxypropyl)]phenylpiperazine,
(65) 1-ethyl-4-[3-(2-fluorophenyl)-4-methoxy-5-propyl]phenylpiperazine,
(66) 1-ethyl-4-[3-(4-trifluoromethylphenyl)-4-methoxy-5-propyl]phenylpiperazine,
(67) l-ethyl-4-[3-phenyl-4-methoxy-5-(1-fluoroisopropyl)]phenylpiperazine,
(68) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxyisopropyl)]phenylpiperazine,
(69) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-fluoropropyl)]phenylpiperazine,
(70) 1-ethyl-4-(3-phenyl-4-methoxy-5-cyano)phenylpiperazine,
(71) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-furanyl)]-phenylpiperazine,
(72) 1-ethyl-4-[3-(2,4-difluorophenyl)-4-methoxy-5-propyl]phenylpiperazine,
(73) 1-ethyl-4-(3-phenyl-4-methoxy-5-phenylacetyl)-phenylpiperazine,
(74) 1-ethyl-4-[3-phenyl-4-methoxy-5-(4-fluorophenyl)acetyl]phenylpiperazine,
(75) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxyphenethyl)]phenylpiperazine,
(76) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-tetrahydrofuranyl)]phenylpiperazine,
(77) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-fluorophenethyl)]phenylpiperazine,
(78) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridyl)]-phenylpiperazine,
(79) 1-ethyl-4-{3-phenyl-4-methoxy-5-[4-fluoro-(1-hydroxyimino)phenethyl]}phenylpiperazine,
(80) 1-ethyl-4-{3-phenyl-4-methoxy-5-[1-fluoro-2-(2-pyridyl)ethyl]}phenylpiperazine,
(81) 1-ethyl-4-(3-phenyl-4-methoxy-5-(1-propenyl)]-phenylpiperazine,
(82) 1-ethyl-4-[3-(3-fluorophenyl)-4-methoxy-5-propyl]phenylpiperazine,
(83) 1-ethyl-4-(3-phenyl-4-methoxy-5-hydroxymethyl)-phenylplperazine,
(84) 1-ethyl-4-[3-phenyl-4-methoxy-5-(4-pyridyl)-acetyl]phenylpiperazine,

(85) l-ethyl-4-(3-phenyl-4-methoxy-5-methanesulfinyl)phenylpiperazine,
(86) 1-ethyl-4-(3-phenyl-4-methoxy-5-ethanesulfinyl)phenylpiperazine,
(87) 1-ethyl-4-(3-phenyl-4-methoxy-5-formyl)-phenylpiperazine,
(88) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1,3-dioxan-2-yl)phenylpiperazine,
(89) 1-ethyl-4-(3-phenyl-4-methoxy-5-cyclopropaneacetyl)phenylpiperazine,
(90) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridylcarbonyl)]phenylpiperazine,
(91) 1-ethyl-4-(3-phenyl-4-methoxy-5-amino)phenylpiperazine,
(92) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-ethoxycarbonylethyl)]phenylpiperazine,
(93) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridyl)-hydroxymethyl]phenylpiperazine,
(94) 1-ethyl-4-(3-phenyl-5-propyl-6-methoxy)phenylpiperazine.
(95) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-acetylethyl)]phenylpiperazine,
(96) 1-ethyl-4-{3-phenyl-4-methoxy-5-[1-(2-pyridylmethoxy)propyl]}phenylpiperazine,
(97) 1-ethyl-4-[3-(2-tolyl)-4-methoxy-5-propyl]-phenylpiperazine,
(98) 1-ethyl-4-(3-phenyl-4-methoxy-5-propylamino)-phenylpiperazine,
(99) 1-(3-phenyl-4-hydroxy-5-phenylacetyl)phenylpiperazine,
(100) 1-ethyl-4-(3-phenyl-4-methoxy-5-benzylsulfinyl)phenylpiperazine,
(101) 1-ethyl-4-(3-phenyl-4-methoxy-5-benzenesulfonylamino)phenylpiperazine,
(102) 1-ethyl-4-{3-phenyl-4-methoxy-5-[1-fluoro-2-(4-pyridyl)ethyl]}phenylpiperazine,
(103) 1-ethyl-4-[3-phenyl-4-methoxy-5-(N-ethanesulfonyl-N-methylamino)]phenylpiperazine,
(104) 1-ethyl-4-(3-phenyl-4-methoxy-5-ethylaminosulfonyl)phenylpiperazine,
(105) 1-ethyl-4-(3-phenyl-4-methoxy-5-aminosulfonyl)phenylpiperazine,
(106) 1-(3-phenyl--4-methoxy-5-phenylacetyl)-phenylpiperazine,
(107) 1-benzyl-4-(3-phenyl-4-methoxy-5-phenylacetyl)phenylpiperazine,
(108) 1-ethyl-4-[3-phenyl-4-chloro-5-(l-fluoropropyl)]phenylpiperazine,
(109) 1-hydroxyethyl-4-(3-phenyl-4-methoxy-5-phenylacetyl)phenylpiperazine,
(110) 1-ethyl-4-[3-phenyl-5-(1-fluoropropyl)]-phenylpiperazine,
(111) 1-ethyl-4-(3-phenyl-5-propionyl)phenylpiperazine,
(112) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(113) 1-ethyl-4-[3-(2-methoxyphenyl)-4-methoxy-5-propyl]phenylpiperazine,
(114) 1-ethyl-4-(3-phenyl-4-methoxy-5-ethanesulfonyl)phenylpiperazine,
(115) 1-ethyl-4-(3-phenyl-4-methoxy-5-dimethylaminosulfonyl)phenylpiperazine,
(116) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-pyrrolidinylsulfonyl)]phenylpiperazine,
(117) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(2,2,2-trifluoroethyl)sulfonylamino]phenylpiperazine,
(118) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(4-fluorophenylsulfonylamino)]phenylpiperazine,
(119) 1-ethyl-4-[3-phenyl-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine,
(120) 1-ethyl-4-(3-phenyl-4-chloro-5-ethanesulfonyl)phenylpiperazine,
(121) 1-ethyl-4-(3-phenyl-4-chloro-5-propionyl)-phenylpiperazine,
(122) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-pyrrolidylsulfonyl)]phenylpiperazine,
(123) 1-ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-(1-fluoropropyl)}phenylpiperazine,
(124) 1-ethyl-4-[3-(2-methoxyphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(125) 1-ethyl-4-[3-(2,4-difluorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(126) 1-ethyl-4-[3-(2-methoxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(127) 1-ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-cyclopropaneaminosulfonyl}phenylpiperazine,
(128) 1-ethyl-4-[3-phenyl-4-chloro-5-(1-methylpropyl)]phenylpiperazine,
(129) 1-ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-cyclopropylmethylsulfonyl}phenylpiperazine,
(130) 1-ethyl-4-(3-phenyl-4-fluoro-5-ethanesulfonyl)phenylpiperazine,
(131) 1-[3-(4-pyridyl)propyl]-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(132) 1-propyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(133) 1-ethyl-4-[3-(2-hydroxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(134) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(135) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-dimethylaminosulfonyl]phenylpiperazine,
(136) 1-ethyl-4-[3-(2-tolyl)-4-fluoro-5-methanesulfonyl]phenylpiperazine,
(137) 1-ethyl-4-[3-(2-chloro-4-fluorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(138) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-ethylpropyl)]phenylpiperazine,
(139) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-methanesulfonyl]phenylpiperazine,
(140) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonyl]phenylpiperazine,
(141) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoro-4-pentenyl)]phenylpiperazine,
(142) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propylaminosulfonyl]phenylpiperazine,

(143) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine,
(144) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(2,2,2-trifluoroethyl)sulfonylamino]phenylpiperazine,
(145) 1-ethyl-4-[3-(2-tolyl)-4-cyano-5-(1-fluoropropyl)]phenylpiperazine,
(146) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(3-chloropropyl)sulfonylamino]phenylpiperazine,
(147) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-phenylaminosulfonyl]phenylpiperazine,
(148) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-benzyloxymethyl]phenylpiperazine,
(149) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propoxymethyl]phenylpiperazine,
(150) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(4-pyridyl)-methoxymethyl]phenylpiperazine,
(151) 1-ethyl-4-(3-phenyl-4-methoxy-5-propanesulfonyl)phenylpiperazine,
(152) 1-ethyl-4-(3-phenyl-4-methoxy-5-butanesulfonyl)phenylpiperazine,
(153) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-fluoroethane)sulfonyl]phenylpiperazine,
(154) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-ethoxymethyl]phenylpiperazine,
(155) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-(1-hydroxybutyl)]phenylpiperazine,
(156) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-allyloxymethyl]phenylpiperazine,
(157) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-cyclopropylmethoxymethyl]phenylpiperazine,
(158) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-pyrrolidinyl)]phenylpiperazine,
(159) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine,
(160) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-benzylsulfonylamino]phenylpiperazine,
(161) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-propanesulfonyl]phenylpiperazine,
(162) 1-ethyl-4-{3-phenyl-4-methoxy-5-[3-(4-fluorophenoxy)propane]sulfonyl}phenylpiperazine,
(163) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-isopropylsulfonylamino]phenylpiperazine,
(164) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-cyanoethylsulfonyl)]phenylpiperazine,
(165) 1-ethyl-4-(3-phenyl-4-chloro-5-propanesulfonylamino)phenylpiperazine,
(166) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-difluoromethyl]phenylpiperazine,
(167) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1,1-difluoropropyl)]phenylpiperazine,
(168) 1-ethyl-4-[3-(4-methoxyphenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(169) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-methanesulfonylamino]phenylpiperazine,
(170) 1-ethyl-4-[3-(2,4-dichlorophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(171) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propanedithio]phenylpiperazine,
(172) 1-ethyl-4-[3-phenyl-4-chloro-5-(1,3-dithian-2-yl)]phenylpiperazine,
(173) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylaminomethyl]phenylpiperazine,
(174) 1-methyl-4-[3-(4-fluorophenyl)-4-methoxy-5-propanesulfonyl]phenylpiperazine,
(175) 1-ethyl-4-[3-(2-ethylphenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(176) 1-hydroxyethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(177) 1-ethyl-4-[3-(2-formylphenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(178) 1-ethyl-4-[3-(2-cyanophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(179) 1-(2-pyridylethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(180) 1-(2-pyridylmethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(181) 1-(3-pyridylmethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(182) 1-(4-pyridylethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(183) 1-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl)phenylpiperazine,
(184) 1-(2-fluoroethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl)phenylpiperazine,
(185) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-propenyl)]phenylpiperazine,
(186) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-chloropropyl)]phenylpiperazine,
(187) 1-methyl-4-[3-phenyl-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(188) 1-methyl-4-[3-(2-hydroxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(189) 1-ethyl-4-[3-(2-fluoromethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(190) 1-methyl-4-{3-(2-fluoromethylphenyl)-4-chloro-5-[1-fluoropropyl]}phenylpiperazine,
(191) 1-ethyl-4-(3-[2-(4-fluorotolyl)]-4-chloro-5-[1-fluoropropyl]}phenylpiperazine,
(192) 1-[2-(2-pyridyl)ethyl]-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(193) 1-[2-(2-pyridyl)ethyl]-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(194) 1-ethyl-4-[3-(2,6-xylyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(195) 1-ethyl-4-{3-(2-trifluoromethylphenyl)-4-chloro-5-[1-fluoropropyl]}phenylpiperazine,
(196) 1-ethyl-4-[3-(2-ethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(197) 1-(2-hydroxyethyl)-4-[3-(2-ethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(198) 1-(2-hydroxyethyl)-4-{3-(2-trifluoromethylphenyl)-4-chloro-5-[1-fluoropropyl]}phenylpiperazine,
(199) 1-methyl-4-{3-(2-tolyl)-4-chloro-5-[1-fluoropropyl]}phenylpiperazine, and
(200) 1-(2-hydroxyethyl)-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-[1-fluoropropyl]}phenylpiperazine.

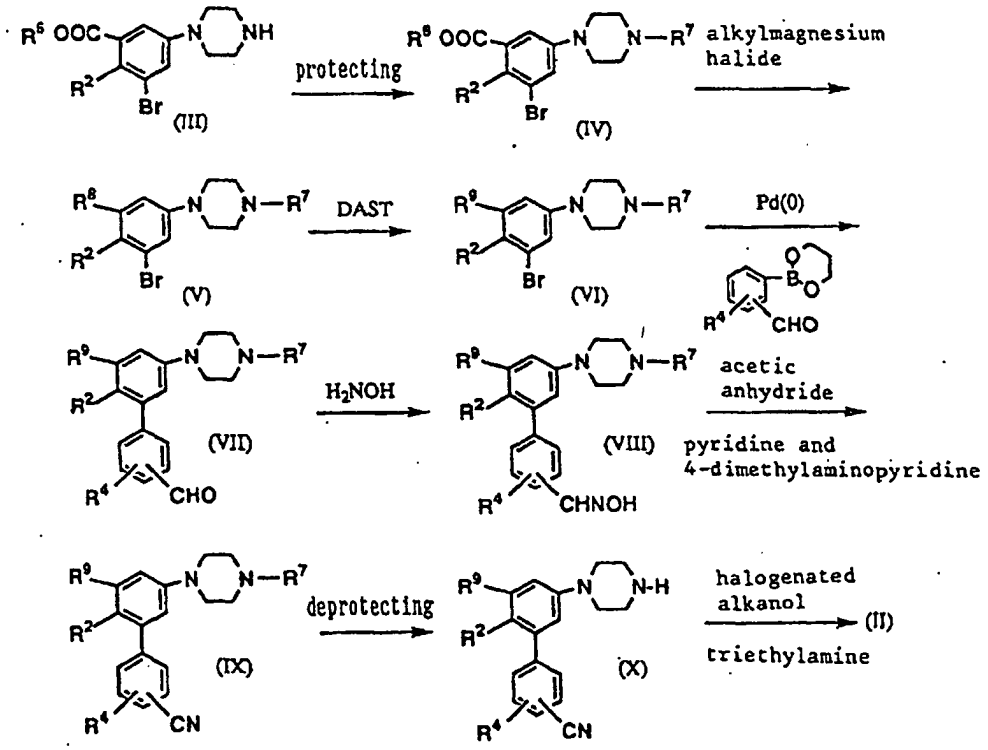
[0020] The biphenyl derivative represented by the formula (I) or (II) according to the present invention can be prepared by the following processes, though the processes for the preparation of the derivative are not limited to them.

(1) biphenyl derivatives represented by the formula (I) or (II) wherein R^1 is a halogenated lower alkyl group, R^3 is a cyano group, R^5 is a hydroxy lower alkyl group

[0021] A phenylpiperazine derivative (III) is protected to form a protected phenylpiperazine derivative (IV); the derivative (IV) is reacted with an alkylmagnesium halide to form a protected hydroxyalkylphenylpiperazine derivative (V); the derivative (V) is reacted with a halogenating agent such as hexafluoropropene diethylamine, diethylaminosulfur trifluoride (hereinafter abbreviated to "DAST"), thionyl chloride and sulfuryl chloride to form a protected halogenated alkylphenylpiperazine derivative (VI); the derivative (VI) is reacted with 2-(1,3,2-dioxaborinan-2-yl)benzaldehyde in the presence of tetrakis(triphenylphosphine)palladium (0) and cesium carbonate to form a protected halogenated alkylbiphenylpiperazine derivative (VII); the derivative (VII) is reacted with hydroxyamine to form a protected halogenated alkyl oxime biphenylpiperazine derivative (VIII); the derivative (VIII) is reacted with acetic anhydride in the presence of pyridine and 4-dimethylaminopyridine to form a protected halogenated alkylcyanobiphenylpiperazine derivative (IX); the derivative (IX) is treated with an acid to form a halogenated alkylcyanobiphenylpiperazine derivative (X); and the derivative (X) is reacted with a halogenated alkanol.

[0022] The protected hydroxyalkylphenylpiperazine derivative (V) and the compounds subsequent thereto may each have an asymmetric carbon atom in its molecule, and the objective compound can be prepared as an optically active substance either by optical resolution of the corresponding compound or by asymmetric synthesis, if necessary. In the optical resolution, optically active cis-2-benzamidocyclohexane carboxylic acid (hereinafter abbreviated to "cis acid"), optically active dibenzoyl tartaric acid (hereinafter abbreviated to "DBTA"), di-p-toluoyl tartaric acid (hereinafter abbreviated to "DTTA") and the like may be used as a reagent for optical resolution.

[0023] This process is illustrated by the following reaction scheme:



wherein R^2, R^4, R^6, R^7, R^8 and R^9 are each as defined above.

(2) biphenyl derivatives represented by the formula (I) or (II) wherein R^1 is a halogenated lower alkyl group; R^3 is one of various groups including cyano group; R^5 is one of various groups including hydroxy lower alkyl group;

[0024] Such biphenyl derivatives can be prepared by one of the following three processes:

(i) a nitrobenzoic acid ester derivative (XIV) is hydrolyzed and the resulting product is reacted with a chlorinating agent such as oxalyl chloride to form a nitrobenzoyl chloride derivative (XV); this derivative (XV) is reacted with an alkylmalonic acid ester in the presence of a base to form a malonic acid ester derivative (XVI); this derivative (XVI) is treated with an acid or a base to form an acylnitrobenzene derivative (XVII); this derivative (XVII) is reduced with sodium borohydride, diisopinocanephenylboron B-chloride (Dip-chloride) or the like; the resulting product is reacted with a halogenating agent to form a halogenated alkylnitrobenzene derivative (XVIII): this derivative (XVIII) is reduced into a halogenated alkylaniline derivative (XIX); this derivative (XIX) is reacted with bis(2-chloroethyl) amine to form a halogenated alkylphenylpiperazine derivative (XX); this derivative (XX) is reacted with a 2-(1,3,2-dioxaborinan-2-yl)benzene derivative or the like in the presence of triphenylphosphinepalladium [$Pd(PPh_3)_4$] and tripotassium phosphate to form a biphenylpiperazine derivative (XXI); and this derivative (XXI) is reacted with a halogenated alkanol or the like.

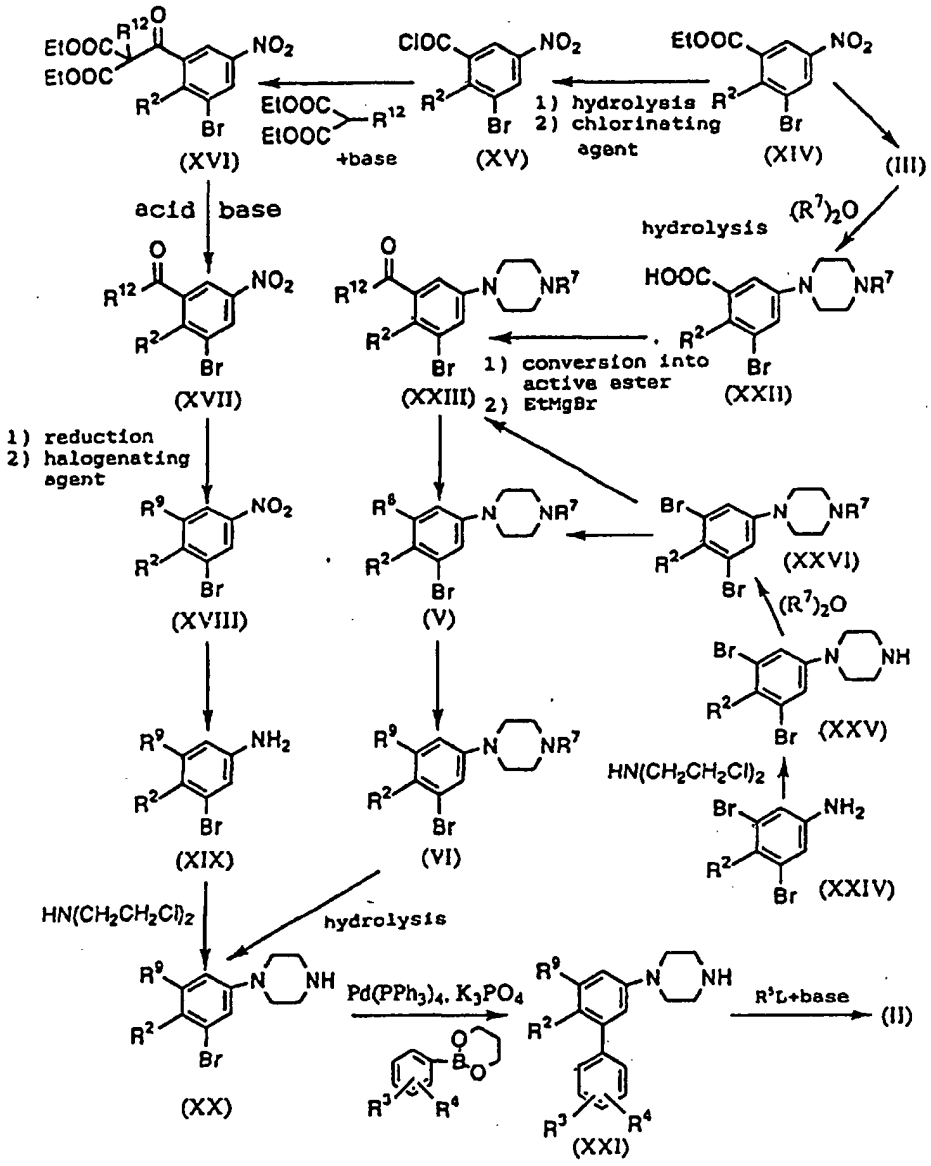
The halogenated alkylnitrobenzene derivative (XVIII) and the compounds subsequent thereto may each have an asymmetric carbon atom in its molecule, and the objective compound can be prepared as an optically active substance either by optical resolution of the corresponding compound or by asymmetric synthesis, if necessary.

(ii) a phenylpiperazine derivative (III) derived from a nitrobenzoic acid ester derivative (XIV) is protected to form a protected piperazylbenzoic acid derivative (XXII); this derivative (XXII) is reacted with 2-mercaptopyridine or the like to form an active ester; this ester is reacted with a Grignard reagent such as alkylmagnesium bromide to form a protected acylphenylpiperazine derivative (XXIII); this derivative (XXIII) is reduced with sodium borohydride or the like to form a protected hydroxyalkylphenylpiperazine derivative (V); this derivative (V) is reacted with a halogenating agent to form a protected halogenated alkylphenylpiperazine derivative (VI); this derivative (VI) is deprotected to form a halogenated alkylphenylpiperazine derivative (XX); and this derivative (XX) is treated in a similar manner to that of the process (i).

The protected hydroxyalkylphenylpiperazine derivative (V) and the compounds subsequent thereto may each have an asymmetric carbon atom in its molecule, and the objective compound can be prepared as an optically active substance either by optical resolution of the corresponding compound or by asymmetric synthesis, if necessary.

(iii) a dibromoaniline derivative (XXIV) is reacted with bis(2-chloroethyl)amine to form a dibromophenylpiperazine derivative (XXV); this derivative (XXV) is protected to form a protected dibromophenylpiperazine derivative (XXVI); this derivative (XXVI) is converted into a protected hydroxyalkylphenylpiperazine derivative (V) either by reacting the derivative (XXVI) with a base and an acid anhydride to form a protected acylphenylpiperazine derivative (XXIII) and converting the derivative (XXIII) into the derivative (V) or by reacting the derivative (XXVI) with a base and a lower aliphatic aldehyde; and this derivative (V) is treated in a similar manner to that of the process (ii).

[0025] These processes (i) to (iii) can be illustrated by the following reaction scheme:

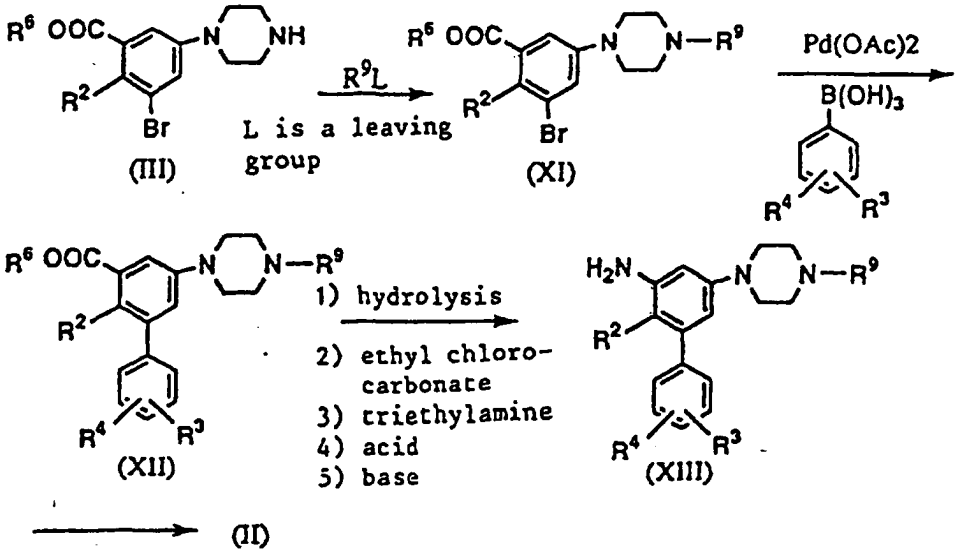


wherein R^2, R^3, R^4, R^7 and R^9 are each as defined above; R^{12} represents a lower alkyl group; L represents a leaving group; and Ph represents a phenyl group.

(3) biphenyl derivatives represented by the formula (I) or (II) wherein R^1 is a lower alkylsulfonylamino group, R^3 and R^5 are the same or different from each other and each is a lower alkyl group or the like;

[0026] A phenylpiperazine derivative (III) is reacted with an alkyl halide to form a phenylalkylpiperazine derivative (XI); the derivative (XI) is reacted with tolylboric acid in the presence of palladium acetate to form a biphenylalkylpiperazine derivative (XII); the derivative (XII) is hydrolyzed; the product of this hydrolysis is reacted with ethyl chlorocarbonate in the presence of triethylamine; the resulting product is reacted with sodium azide and a base successively to form an aminobiphenylalkylpiperazine derivative (XIII); and the derivative (XIII) is reacted with an alkylsulfonyl halide.

[0027] This process is illustrated by the following reaction scheme:



wherein R^2, R^3, R^4, R^6 and R^9 are each as defined above.

[0028] The biphenyl derivatives of the present invention can be prepared from, e.g., known 2-phenyl-[1,3,2]-dioxaborinane derivatives and known phenylboric acid derivatives of which specific examples will be described below according to one of the production processes described above.

[0029] The following 2-phenyl-[1,3,2]-dioxaborinane derivatives and phenylboric acid derivatives can also be prepared according to known synthetic processes.

Specific examples of 2-phenyl-[1,3,2]-dioxaborinane derivatives (those described in the brackets are CAS registry numbers)

[0030]

(1) 2-phenyl-[1,3,2]-dioxaborinane [4406-77-3],
(2) 2-(4-fluorophenyl)-[1,3,2]-dioxaborinane [156942-21-1],
(3) 2-(4-bromophenyl)-[1,3,2]-dioxaborinane [54947-91-0],
(4) 2-(4-methoxyphenyl)-[1,3,2]-dioxaborinane [155826-85-0],
(5) 2-(4-cyanophenyl)-[1,3,2]-dioxaborinane [152846-62-3],
(6) 2-(2-methoxyphenyl)-[1,3,2]-dioxaborinane [141522-26-1], and
(7) 2-(2,4-dichlorophenyl)-[1,3,2]-dioxaborinane [73852-21-8].

Specific examples of phenylboric acid derivatives (those described in the brackets are CAS registry numbers)

[0031]

(1) phenylboric acid [98-80-6],
(2) 2-fluorophenylboric acid [1993-03-9],
(3) 3-fluorophenylboric acid [768-35-4],
(4) 4-fluorophenylboric acid [1765-93-1],
(5) 2-chlorophenylboric acid [3900-89-8],
(6) 3-chlorophenylboric acid [63503-60-6],
(7) 4-chlorophenylboric acid [1679-18-1],
(8) 3-bromophenylboric acid [89598-96-9],
(9) 4-bromophenylboric acid [5467-74-3 or 130869-99-7].
(10) 4-iodophenylboric acid [5122-99-6],
(11) 2-cyanophenylboric acid [138642-62-3],

(12) 3-cyanophenylboric acid [150255-96-2],
(13) 4-cyanophenylboric acid [126747-14-6],
(14) 2-trifluoromethylphenylboric acid [1423-27-4],
(15) 3-trifluoromethylphenylboric acid [1423-26-3],
(16) 4-trifluoromethylphenylboric acid [128796-39-4],
(17) 2-ethylphenylboric acid [90002-36-1],
(18) 3-ethylphenylboric acid [90555-65-0],
(19) 4-ethylphenylboric acid [63139-21-9],
(20) 2-formylphenylboric acid [40138-16-7],
(21) 3-formylphenylboric acid [87199-16-4],
(22) 4-formylphenylboric acid [87199-17-5],
(23) 2-hydroxyphenylboric acid [87199-14-2],
(24) 3-hydroxyphenylboric acid [87199-15-3],
(25) 4-hydroxyphenylboric acid [59106-93-2],
(26) 2-methoxyphenylboric acid [5720-06-9],
(27) 3-methoxyphenylboric acid [10365-98-7],
(28) 4-methoxyphenylboric acid [5720-07-0],
(29) 2,4-dichlorophenylboric acid [68716-47-2],
(30) 2,3-difluorophenylboric acid [121219-16-7],
(31) 2,3,4-trimethoxyphenylboric acid [118062-05-8],
(32) 2-fluoro-3-trifluoromethylphenylboric acid [157834-21-4],
(33) 3,4-dichlorophenylboric acid [151169-75-4],
(34) 2,3-dichlorophenylboric acid [151169-74-3],
(35) 3-trifluoromethyl-4-methoxyphenylboric acid [149507-36-8],
(36) 3-fluoromethyl-4-methoxyphenylboric acid [149507-26-6],
(37) 3-chloro-4-fluorophenylboric acid [144432-85-9],
(38) 3-fluoro-4-chlorophenylboric acid [137504-86-0],
(39) 2,4-difluorophenylboric acid [144025-03-6],
(40) 2,4-di(trifluoromethyl)phenylboric acid [153254-09-2],
(41) 3-methoxy-4-chlorophenylboric acid [89694-47-3],
(42) 2,4-dimethoxyphenylboric acid [133730-34-4],
(43) 3,4-dimethoxyphenylboric acid [122775-35-3],
(44) 2,3-dimethoxyphenylboric acid [40972-86-9],
(45) 2-formyl-4-methoxyphenylboric acid [139962-95-1], and
(46) 3-formyl-4-methoxyphenylboric acid [121124-97-8].

[0032] Although the biphenyl derivative according to the present invention may be present as a stereoisomer, the present invention is not limited in this respect, but the derivative may be any of the stereoisomers thereof or a mixture of them. Further, the biphenyl derivative according to the present invention may be any of the geometrical isomers thereof or a mixture of them.

[0033] The pharmacologically acceptable salt of the biphenyl derivative according to the present invention includes inorganic acid addition salts such as hydrochloride, sulfate, nitrate, hydrobromide, hydroiodide, perchlorate and phosphate; organic acid addition salts such as oxalate, maleate, fumarate and succinate; sulfonic acid addition salts such as methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and camphorsulfonate; and amino acid addition salts.

[0034] The present invention also relates to the phenypiperazine derivative represented by the above formula (XXVII) or salt thereof. The kind of the salt is not limited. The phenylpiperazine derivative represented by the formula (XXVII) is novel and is useful as an intermediate for the preparation of the biphenyl derivative represented by the formula (I) or (II) according to the present invention.

[0035] Specific examples of the phenylpiperazine derivative represented by the formula (XXVII) include the following compounds, though the derivative (XXVII) is not limited to them:

(1) 1-[3-bromo-4-chloro-5-(1-hydroxyethyl)]phenylpiperazine,
(2) 1-[3-bromo-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine,
(3) 1-[3-bromo-4-chloro-5-(1-hydroxybutyl)]phenylpiperazine,
(4) 1-[3-bromo-4-chloro-5-(1-hydroxypentyl)]phenylpiperazine,
(5) 1-[3-bromo-4-chloro-5-(1-hydroxyhexyl)]phenylpiperazine,
(6) 1-hydroxymethyl-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,

(7) 1-hydroxyethyl-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(8) 1-hydroxypropyl-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(9) 1-hydroxybutyl-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(10) 1-hydroxypentyl-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(11) 1-hydroxyhexyl-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(12) 1-hydroxyethyl-4-[3-bromo-4-chloro-5-(1-chloropropyl)]phenylpiperazine,
(13) 1-hydroxyethyl-4-[3-bromo-4-chloro-5-(1-bromopropyl)]phenylpiperazine,
(14) 1-hydroxyethyl-4-[3-bromo-4-chloro-5-(1-iodopropyl)]phenylpiperazine,
(15) 1-(t-butoxy)carbonyl-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(16) 1-ethoxycarbonyl-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(17) 1-benzyloxycarbonyl-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(18) 1-formyl-4-[3-bromo-4-chloro-5-(1-fluoropropyl)] phenylpiperazine,
(19) 1-acetoxy-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(20) 1-benzyl-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(21) 1-(2-trimethylsilyloxyethyl)-4-[3-bromo-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine,
(22) 1-(2-trimethylsilyloxyethyl)-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(23) 1-(2-trimethylsilyloxyethyl)-4-[3-bromo-4-chloro-5-(1-chloropropyl)]phenylpiperazine,
(24) 1-(2-trimethylsilyloxyethyl)-4-[3-bromo-4-chloro-5-(1-bromopropyl)]phenylpiperazine,
(25) 1-(2-trimethylsilyloxyethyl)-4-[3-bromo-4-chloro-5-(1-iodopropyl)]phenylpiperazine,
(26) 1-(3,5-dibromo-4-chloro)phenylpiperazine,
(27) 1-(t-butoxycarbonyl)-4-(3,5-dibromo-4-methoxy)-phenylpiperazine,
(28) 1-(t-butoxycarbonyl)-4-(3,5-dibromo-4-chloro)-phenylpiperazine,
(29) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine,
(30) 1-(3-bromo-4-chloro-5-ethoxycarbonyl)phenylpiperazine,
(31) 1-(t-butoxycarbonyl)-4-(3-bromo-4-chloro-5-ethoxycarbonyl)phenylpiperazine,
(32) 1-ethyl-4-(3-bromo-4-chloro-5-ethoxycarbonyl)-phenylpiperazine,
(33) 1-[3-bromo-4-chloro-5-(1-propenyl)]phenylpiperazine,
(34) 1-(t-butoxycarbonyl)-4-(3-bromo-4-chloro-5-carboxy)phenylpiperazine,
(35) 1-(t-butoxycarbonyl)-4-[3-bromo-4-chloro-5-(2-pyridylthio)carbonyl]phenylpiperazine, and
(36) 1-(t-butoxycarbonyl)-4-(3-bromo-4-chloro-5-propionyl)phenylpiperazine.

[0036] The compound of the present invention exhibits an extremely high LD_{50} value and extremely high safeness.

[0037] The biphenyl derivative or the pharmacologically acceptable salt thereof according to the present invention may be used as an active ingredient of a therapeutic and ameliorative agent for a mental disorder. Examples of the mental disorder include cerebrovascular disorder, aggressive behavior due to senile dementia, mental excitation, poriomania, delirium, hallucination, hyperkinesia, schizophrenia, emotional disturbance, depression, neurosis, psychophysiologic disorder and anxiety neurosis. In other words, the diseases against which the biphenyl derivative or the pharmacologically acceptable salt thereof according to the present invention may be clinically applicable are those against which dopamine 2 receptor antagonism and/or serotonin 2 receptor antagonism is efficacious.

[0038] The dosage form of the compound of the present invention include preparations for oral administration such as powder, fine granule, granule, tablet, coated tablet and capsule; external preparations such as ointment, plaster and suppository; and injection. That is, a pharmacological composition of the present invention comprises a therapeutically or amelioratively effective amount of the biphenyl derivative or the pharmacologically acceptable salt thereof described above and a pharmacologically acceptable vehicle.

[0039] These preparations can be each prepared by the use of a conventional vehicle, filler or carrier according to a conventional method. A preparation for oral administration according to the present invention is prepared by adding a vehicle or filler and, if necessary, a binder, disintegrator, lubricant, color and/or corrigent to the biphenyl derivative or the pharmaceutically acceptable salt thereof and shaping the obtained mixture into a powder, fine granule, granule, tablet, coated tablet, capsule or the like.

[0040] Examples of the vehicle or filler include lactose, corn starch, sucrose, glucose, mannitol, sorbitol, crystalline cellulose and silicon dioxide; those of the binder include polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, polypropylene glycol-polyoxyethylene block copolymer and meglumine; those of the disintegrator include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogen carbonate, calcium citrate, dextrin, pectin and calcium carboxymethylcellulose; those of the lubricant include magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils; those of the color include those authorized as pharmaceutical additives; and those of the corrigent include cocoa powder, menthol, aromatic powder, mentha oil, borneol and powdered cinnamon bark. Of course, the tablet and granule may be suitably coated with sugar or the like, if necessary.

[0041] An injection according to the present invention is prepared by adding a pH modifier, solubilizing agent, isotonicity agent and, if necessary, an auxiliary solubilizer and/or stabilizer to the biphenyl derivative or the pharmaceutically acceptable salt thereof, and formulating the obtained mixture in a conventional manner.

[0042] The method for preparing an external preparation according to the present invention is not limited, but may be any ordinary one. The base material to be used in this preparation includes various materials conventionally used in the preparation of drugs, quasi drugs, cosmetics and so on.

[0043] Specific examples of the base material to be used in the external preparation include animal and vegetable oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals and purified water, and examples of the material to be optionally used at need include pH modifiers, antioxidants, chelating agents, antiseptics, antifungal substances, coloring matters and fragrances, though the material is not limited to them. The external preparation may further contain a differentiation-inducing agent, a blood flow accelerator, a disinfectant an antiphlogistic, a cell activator, a vitamin, an amino acid, a humectant and/or a keratolytic. The above base materials are each used in such an amount as to give a concentration ordinarily predetermined in the preparation of an external preparation.

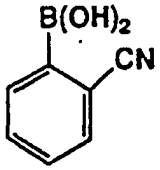
[0044] The dose of the biphenyl derivative or the pharmacologically acceptable salt thereof according to the present invention varies depending upon symptom and degree thereof, age, complication and so on, and therefore cannot be limited. Further, the dose varies also depending upon the kind of the salt or route of administration. The dose per adult a day is generally 0.01 to 1000 mg, preferably 0.1 to 500 mg, still more preferably 0.5 to 100 mg, which is administered orally, intravenously, as a suppository or transcutaneously.

[0045] The preparation processes of a 2-phenyl-[1,3,2]-dioxaborinane derivative and a phenylboric acid derivative which are necessary for carrying out the present invention will now be described specifically as Preparative Examples. Other derivatives can also be prepared in manners similar thereto.

Preparative Examples

Preparative Example 1 Synthesis of 2-cyanophenylboric acid

[0046]



[0047] 12.4 ml of a 1.6 M solution of t-butyllithium in n-pentane was dropwise added to 23 ml of THF at -76°C in about 10 minutes. Then, a solution of 2.0 g (11.0 mmol) of 2-bromobenzonitrile in 3.0 ml of THF was dropwise added to the resulting mixture at -76°C in about 20 minutes, followed by the dropwise addition of 2.3 ml (19.8 mmol) of trimethoxyborane in 7 minutes. The obtained mixture was stirred at -76°C for 20 minutes, followed by the addition of 13.8 ml of 2N hydrochloric acid. The obtained mixture was stirred at room temperature for 30 minutes and extracted with ethyl acetate. The ethyl acetate phase was washed with water and a saturated brine, dried and distilled to remove the solvent. 15 ml of methylene chloride and 15 ml of n-hexane were added to the obtained residue. The obtained mixture was stirred at room temperature for 30 minutes to give a precipitate. The precipitate was recovered by filtration and dried to give 0.9 g of the title compound (yield: 55.7%).

m.p.; 237~240°C

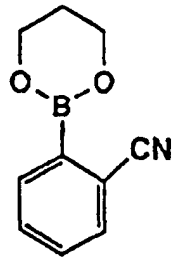
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5~8.1(5H, m), 8.77(1H, m).

^{1}H-NMR(400MHz, $CDCl_3$+D_2O); δ(ppm) 7.56(1H, dd, J=6.2, 7.3Hz), 7.64(1H, dd, J=6.2, 7.3Hz), 7.71(1H, d, J=7.3Hz), 8.05(1H, dd, J=7.3Hz).

IR(cm^{-1}, nujol): 2200

Preparative Example 2 Synthesis of 2-(1,3,2-dioxahorinan-2-yl)benzonitrile

[0048]



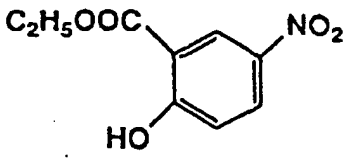
[0049] 543 mg (3.7 mmol) of 2-cyanophenylboric acid was added to a solution of 280 mg (3.7 mmol) of 1,3-propanediol in 5.4 ml of methylene chloride. The obtained mixture was stirred at room temperature for 1.5 hours, followed by the removal of formed water. The obtained mixture was distilled to remove the solvent under reduced pressure to give 0.7 g of the title compound (yield: 100%).
m.p.; 45-48°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 2.11(2H, m), 4.23(4H, d, J=5.5Hz), 7.48(1H, dd, J=7.6, 7.6Hz), 7.54(1H, dd, J=7.6, 7.6Hz), 7.68(1H, d, J=7.6Hz), 7.87(1H, dd, J=7.6Hz).
MS m/z: 188[MH]$^+$.

[0050] Examples will now be given to illustrate the present invention specifically, though it is needless to say that the present invention is not limited to only them.

Examples

Example 1 Synthesis of ethyl 5-nitrosalicylate

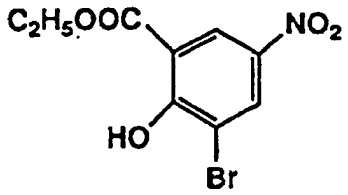
[0051]



[0052] 1.5 kg (8.2 mol) of 5-nitrosalicylic acid was dissolved in 2000 ml of triethyl orthoformate. The obtained solution was refluxed under heating for 3 hours to remove formed ethanol by distillation. The reaction mixture was cooled and then concentrated under reduced pressure. The obtained residue was crystallized from isopropyl ether to give 1.74 kg of the title compound as a colorless crystal.
m.p.; 85°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 11.5(1H, s), 8.9(1H, d), 8.3(1H, d-d), 7.1(1H, d), 4.5(2H, q), 1.5(3H, t).

Example 2 Synthesis of ethyl 3-bromo-5-nitrosalicylate

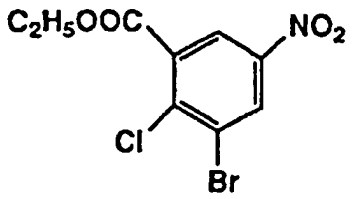
[0053]



[0054] 1.74 kg (8.2 mol) of ethyl 5-nitrosalicylate and 700 g of potassium acetate were dissolved in 5000 ml of acetic acid. 1.312 kg of bromine was dropwise added to the obtained solution at room temperature in one hour. Thereafter, the resulting mixture was further stirred for one hour and then concentrated under reduced pressure. The obtained residue was dissolved in ethyl acetate. The obtained solution was washed with water, dehydrated and concentrated under reduced pressure. The obtained residue was crystallized from isopropyl ether to give 2.38 kg of the title compound as a colorless crystal.
m.p.; 108°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 12.3(1H, s), 8.9(1H, d), 8.6(1H, d), 4.5(2H, q), 1.5(3H, t).

Example 3 Synthesis of ethyl 2-chloro-3-bromo-5-nitrobenzoate

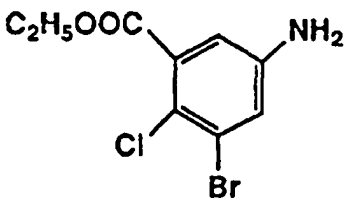
[0055]



[0056] 2.38 kg (8.2 mol) of ethyl 3-bromo-5-nitrosalicylate was dissolved in 3000 ml of DMF, followed by the dropwise addition of 1.26 kg of phosphorus oxychloride at room temperature. The obtained mixture was heated to 90°C and then maintained at that temperature under heating for 10 hours. The obtained mixture was cooled and then concentrated under reduced pressure. The obtained residue was dissolved in ethyl acetate and the obtained solution was washed with water, dehydrated and concentrated under reduced pressure to give 2.25 kg of the title compound as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.6(1H, d), 8.5(1H, d), 4.5(2H, q), 1.4(3H, t).

Example 4 Synthesis of ethyl 2-chloro-3-bromo-5-aminobenzoate

[0057]

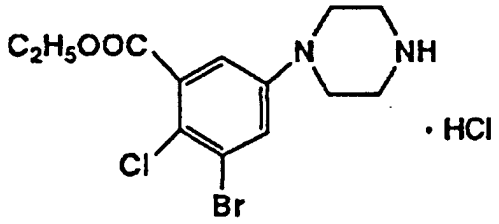


[0058] 2.25 kg (7.3 mol) of ethyl 2-chloro-3-bromo-5-nitrobenzoate was dissolved in a mixture comprising 4000 ml of concentrated hydrochloric acid and 4000 ml of ethanol. 1 kg of powdered iron was added to the obtained solution

in portions so as to maintain the bulk temperature at 80°C. The reaction mixture was cooled, followed by the addition of a saturated brine. The resulting mixture was extracted with ethyl acetate. The organic phase was dried and concentrated under reduced pressure to give 1.8 kg of the title compound as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1(1H, d), 6.9(1H, d), 4.4(2H, q), 3.9(2H, s), 1.2(3H, t).

Example 5 Synthesis of 1-(3-bromo-4-chloro-5-ethoxycarbonyl)phenypiperazine hydrochloride

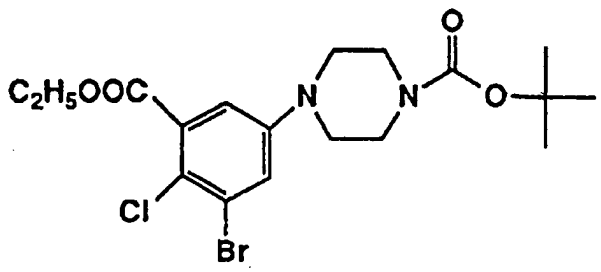
[0059]



[0060] 1.8 kg (6.5 mol) of ethyl 2-chloro-3-bromo-5-aminobenzoate and 1.2 kg (6.7 mol) of bis(2-chloroethyl)amine hydrochloride were dissolved in 5000 ml of o-dichlorobenzene. The obtained solution was refluxed under heating for 3 hours and thereafter cooled by allowing to stand, precipitating a crystal. This crystal was recovered by filtration and dried to give 2.4 kg of the title salt.
m.p.; 250°C or above
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.2(1H, d), 7.1(1H, d), 4.4(2H, q), 3.2(4H, m), 3.0(4H, m), 1.4(3H, t).

Example 6 Synthesis of 1-(t-butoxycarbonyl)-4-(3-bromo-4-chloro-5-ethoxycarbonyl)phenylpiperazine

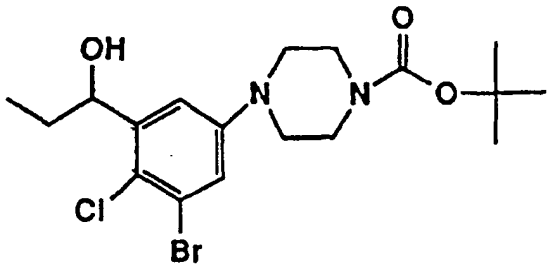
[0061]



[0062] 880 g (2.3 mol) of 1-(3-bromo-4-chloro-5-ethoxycarbonyl)phenypiperazine hydrochloride was suspended in a mixture comprising 500 g (5 mol) of triethylamine and 2000 ml of acetonitrile, followed by the dropwise addition of 500 g of di-t-butyl carbonate under cooling with ice. After the completion of the dropwise addition, the resulting mixture was further stirred at room temperature for one hour and then concentrated. The obtained residue was dissolved in ethyl acetate and the obtained solution was washed with water, dried and concentrated under reduced pressure. The obtained residue was crystallized from isopropyl ether to give 1 kg of the title compound as a colorless crystal.
m.p. ; 115°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.2(1H, d), 7.1(1H, d), 4.4(2H, q), 3.6(4H, t), 3.2(4H, t), 1.5(9H, s), 1.4(3H, t).

Example 7 Synthesis of 1-(t-butoxycarbonyl)-4-[3-bromo-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine

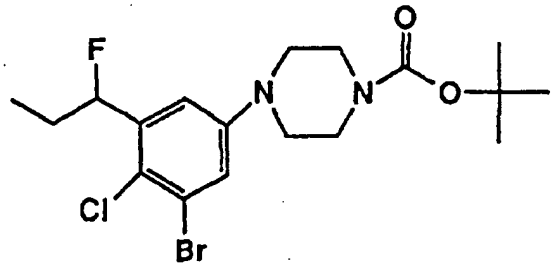
[0063]



[0064] 1 kg (2.23 mol) of 1-(t-butoxycarbonyl)-4-(3-bromo-4-chloro-5-ethoxycarbonyl)phenylpiperazine was dissolved in 4000 ml of THF, followed by the dropwise addition of 5.5 mol of ethylmagnesium bromide under cooling with ice. The obtained mixture was further stirred at room temperature for one hour, followed by the addition of a saturated aqueous solution of ammonium chloride. The obtained mixture was extracted with ethyl acetate. The organic phase was washed with water, dried and concentrated under reduced pressure to give 1 kg of the title compound as a colorless oil. ^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1(1H, d), 7.05(1H, d), 5.0(1H, m), 3.6(4H, t), 3.1(4H, t), 1.6(2H, m), 1.5(9H, s), 1.0(3H, t).

Example 8 Synthesis of 1-(t-butoxycarbonyl)-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

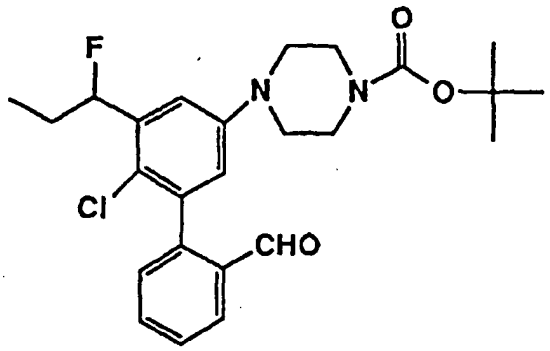
[0065]



[0066] 1 kg (2.3 mol) of 1-(t-butoxycarbonyl)-4-[3-bromo-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine was dissolved in 2000 ml of anhydrous methylene chloride, followed by the dropwise addition of 425 g (2.6 mol) of diethylaminosulfur trifluoride (DAST) at -70°C. After the completion of the dropwise addition, the obtained mixture was further stirred for 30 minutes and poured into water. The aqueous phase was extracted with methylene chloride. The methylene chloride phase was washed with water, dried and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (with ethyl acetate and hexane) to give 900 g of the title compound as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1(1H, d), 7.0(1H, d), 5.7(1H, m), 3.6(4H, m), 3.2(4H, m), 1.8(2H, m), 1.5(9H, m), 1.0(3H, t).

Example 9 Synthesis of 1-(t-butoxycarbonyl)-4-[3-(2-formylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

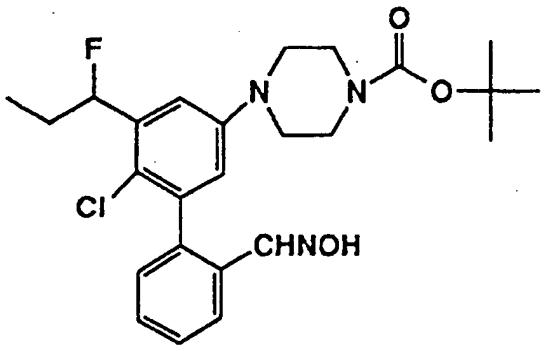
[0067]



[0068] 174 g (0.4 mol) of l-(t-butoxycarbonyl)-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine, 114 g (0.6 mol) of 2-(1,3,2-dioxaborinan-2-yl)benzaldehyde (10) described in Synlett, (3), 207-210, 1992, 1 g of tetrakis(triphenylphosphine)palladium (0) and 195 g (0.6 mol) of cesium carbonate were dissolved in 1000 ml of DMF and the obtained solution was maintained at 100°C for 3 hours to conduct a reaction. The reaction mixture was cooled and then poured into water. The resulting mixture was extracted with ethyl acetate. The organic phase was washed with water, dried and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography and recrystallized from an ethyl acetate/hexane mixture to give 165 g of the title compound as a colorless crystal.
m.p.; 135°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 9.8(1H, d), 8.0(1H, m), 7.7(1H, m), 7.5(1H, m), 7.3(1H, m), 7.1(1H, d), 6.8(1H, d), 5.8(1H, m), 3.6(4H, m), 3.2(4H, m), 1.9(2H, m), 1.5(9H, s), 1.1(3H, t).

Example 10 Synthesis of 1-(t-butoxycarbonyl)-4-[3-(2-hydroxyiminomethylphenyl)-4-chloro-5-(1-fluoropropyl)] phenylpiperazine

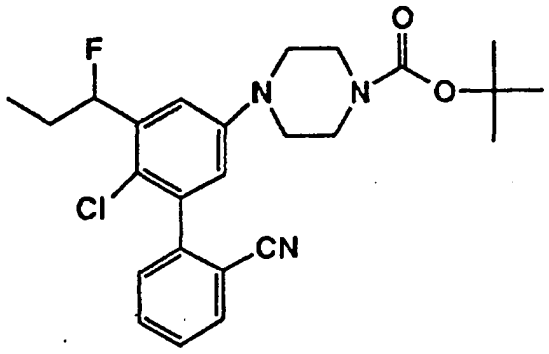
[0069]



[0070] 165 g (0.36 mol) of 1-(t-butoxycarbonyl)-4-[3-(2-formylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine and 50 g (0.72 mol) of hydroxylamine hydrochloride were dissolved in 100 ml of a 5N aqueous solution of NaOH, followed by the addition of 200 ml of ethanol. The obtained mixture was refluxed under heating for 2 hours and thereafter cooled and concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate. The organic phase was washed with water, dried and concentrated under reduced pressure to give 154 g of the title compound as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.0(1H, m), 7.8.(1H, d), 7.6(1H, m), 7.4(1H, m), 7.2(1H, m), 7.1(1H, m), 6.7(1H, m), 5.8(1H, m), 3.6(4H, m), 3.2(4H, m), 1.9(2H, m), 1.5(9H, s), 1.1(3H, t).

Example 11 Synthesis of 1-(t-butoxycarbonyl)-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

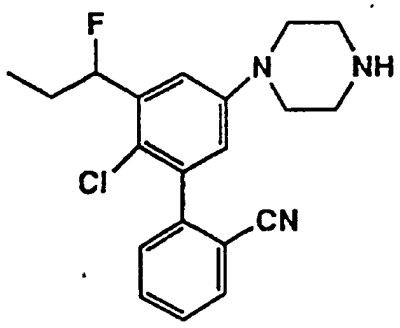
[0071]



[0072] 154 g (0.32 mol) of 1-(t-butoxycarbonyl)-4-[3-(2-hydroxyiminomethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine and 40 g of N,N-dimethylaminopyridine were dissolved in a mixture comprising-100 ml of acetic anhydride and 100 ml of pyridine. The obtained solution was heated to 100°C and maintained at that temperature for one hour to conduct a reaction. The reaction mixture was cooled and then poured into a saturated aqueous solution of sodium hydrogen carbonate. The resulting mixture was extracted with ethyl acetate to give 140 g of the title compound as a colorless crystal.
m.p.; 120°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.8(1H, d), 7.6(1H, t), 7.5(1H, t), 7.4(1H, d), 7.1(1H, d), 6.8(1H, d), 5.9(1H, m), 3.6 (4H, m), 3.2(4H, m), 2.0(2H, m), 1.5(9H, s), 1.1(3H, t).

Example 12 Synthesis of 1-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl]phenylpiperazine

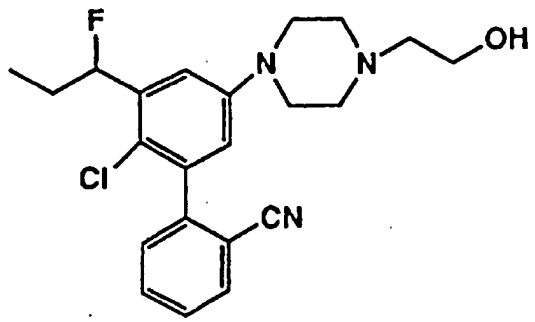
[0073]



[0074] 140 g (0.3 mol) of 1-(t-butoxycarbonyl)-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine was dissolved in a mixture comprising 500 ml of trifluoroacetic anhydride and 500 ml of chloroform. The obtained solution was stirred at 0°C for 5 hours and distilled to remove the solvent. The residue was recrystallized from ethyl acetate and hexane to give 100 g of the title compound as a colorless crystal.
m.p.; 159°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.8(1H, d), 7.6(1H, t), 7.5(1H, t), 7.4(1H, d), 7.1(1H, d), 6.8(1H, d), 5.9(1H, m), 3.5 (1H, b-s), 3.2(4H, m), 3.0(4H, m), 1.9(2H, m), 1.1(3H, t).

Example 13 Synthesis of 1-(2-hydroxyethyl)-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

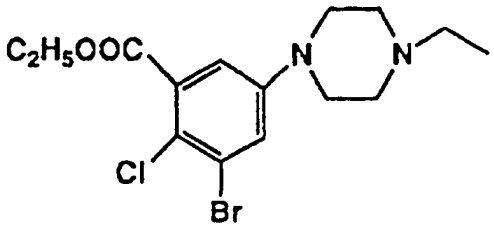
[0075]



[0076] 32.1 g (0.09 mol) of 1-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine, 12.5 g of 2-bromoethanol and 20 g of triethylamine were dissolved in 100 ml of DMF. The obtained solution was heated to 50°C and maintained at that temperature for 24 hours to conduct a reaction. The reaction mixture was cooled and then partitioned between ethyl acetate and water. The ethyl acetate phase was washed with water, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (with methylene chloride/methanol) to give 22 g of the title compound as a colorless oil. This oily product was separated with an optically active column to recover a fraction having a plus angle of rotation. Thus, 10 g of the optically active title compound was obtained as a colorless oil. This product was treated with hydrochloric acid to form a salt thereof. The product was recrystallized from methanol/ether to give a hydrochloride of the title compound as a colorless crystal.
m.p. (hydrochloride); 244-245°C
$[a]_D$=+6.3° (c=1.03, MeOH) (hydrochloride)
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.8(1H, d), 7.6(1H, t), 7.5(1H, t), 7.4(1H, d), 7.1(1H, d), 6.8(1H, d), 5.8(1H, m), 3.7 (2H, t), 3.3(4H, m), 2.7(4H, m), 2.6(2H, t), 1.9(2H, m), 1.1(3H, t).

Example 14 Synthesis of 1-ethyl-4-(3-bromo-4-chloro-5-ethoxycarbonyl)phenylpiperazine

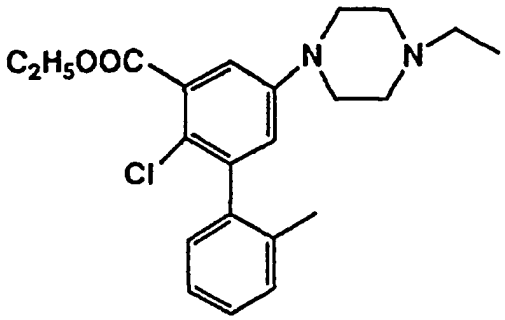
[0077]



[0078] 347 g (1 mol) of 1-(3-bromo-4-chloro-5-ethoxycarbonyl)phenypiperazine hydrochloride was dissolved in 1000 ml of DMF, followed by the addition of 207 g (1.5 mol) of potassium carbonate and 120 g (1.1 mol) of ethyl bromide. The obtained mixture was stirred a room temperature overnight, followed by the addition of water. The resulting mixture was extracted with ethyl acetate. The ethyl acetate phase was washed with water, dried and concentrated under reduced pressure to give 338 g of the title compound as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.2(1H, d), 7.1(1H, d), 4.4(2H, q), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.4(3H, t), 1.1 (3H, t).

Example 15 Synthesis of 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-ethoxylcarbonyl]phenylpiperazine

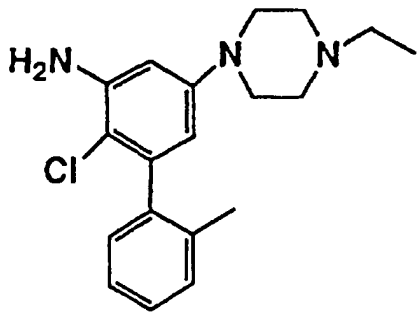
[0079]



[0080] 338 g (0.9 mol) of 1-ethyl-4-(3-bromo-4-chloro-5-ethoxycarbonyl)phenylpiperazine and 136 g (1 mol) of 2-tolylboric acid [$CH_3C_6H_4B(OH)_3$] were dissolved in 3000 ml of DMF, followed by the addition of 20 g of palladium acetate, 55 g of triphenylphosphine and 35 g of triethylamine. The obtained mixture was stirred at 100°C overnight, cooled and partitioned between ethyl acetate and water. The ethyl acetate phase was washed with water, dried and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (with methylene chloride/ethanol) to give 221 g of the title compound as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.0(1H, s), 7.3-7.1(4H, m), 6.8(1H, d), 4.4(2H, q), 3.2(1H, m), 2.6(4H, m), 2.5(2H, q), 1.4(3H, t), 1.2(3H, t), 1.1(3H, t).

Example 16 Synthesis of 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-amino]phenylpiperazine

[0081]

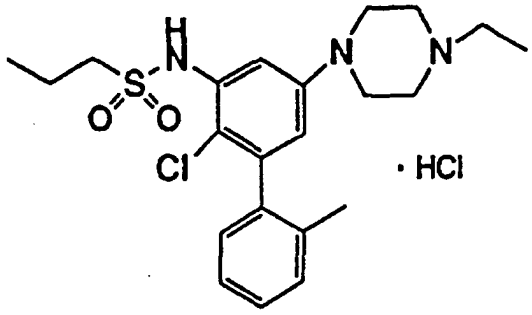


[0082] 193 g (0.5 mol) of 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-ethoxylcarbonyl]phenylpiperazine was dissolved in a mixture comprising 100 ml of 5N NaOH and 500 ml of methanol. The obtained solution was stirred at room temperature for 3 hours and concentrated under reduced pressure. The obtained residue was dissolved in 300 ml of DMF, followed by the addition of 61 g (0.6 mol) of triethylamine. 65 g (0.6 mol) of ethyl chlorocarbonate was dropwise added to the obtained mixture under cooling with ice. The mixture thus obtained was stirred at 0°C for 30 minutes, followed by the addition of 39 g (0.6 mol) of sodium azide. The resulting mixture was subjected to reaction for 2 hours and then poured into water to precipitate a white crystal. This white crystal was recovered by filtration and immediately dissolved in 500 ml of toluene. The obtained solution was heated for one hour, followed by the addition of 300 ml of concentrated hydrochloric acid. The obtained mixture was maintained at 100°C by heating for one hour, cooled, basified with 8N NaOH and extracted with ethyl acetate. The ethyl acetate phase was washed with water, dried and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography to give 83 g of the title compound as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.1(4H, m), 6.3(1H, m), 6.2(1H, m), 4.0(2H, s), 3.2(4H, m), 2.6(4H, m), 2.4(2H,

q), 2.2(3H, m), 1.1(3H, m).

Example 17 Synthesis of 1-ethyl]-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine hydrochloride

[0083]



[0084] 3.3 g (10 mmol) of 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-amino]phenylpiperazine was dissolved in 5 ml of pyridine, followed by the addition of 2.9 g (20 mmol) of propanesulfonyl chloride. The obtained mixture was stirred at room temperature overnight and partitioned between water and ethyl acetate. The ethyl acetate phase was washed with water, dried and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (with methylene chloride/ethanol) to give 2.6 g of the title compound as a colorless oil. This oil was treated with hydrochloric acid to form a hydrochloride thereof, and the product was recrystallized from methanol/ether to give the title compound as a white crystal.

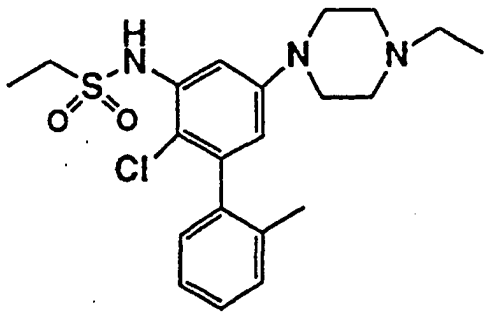
m.p.; 135°C

^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3(4H, m), 7.0(1H, d), 6.8(1H, m), 4.8(1H, t), 4.4(2H, d), 3.2(4H, m), 2.9(2H, m), 2.6(4H, m), 2.5(2H, q), 2.1(3H, s), 1.8(2H, m), 1.1(3H, t), 1.0(3H, t).

[0085] The following compounds were prepared in a similar manner to that of the Example 17 except that the propanesulfonyl chloride was replaced by ethanesulfonyl chloride or butanesulfonyl chloride.

Example 18 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine

[0086]

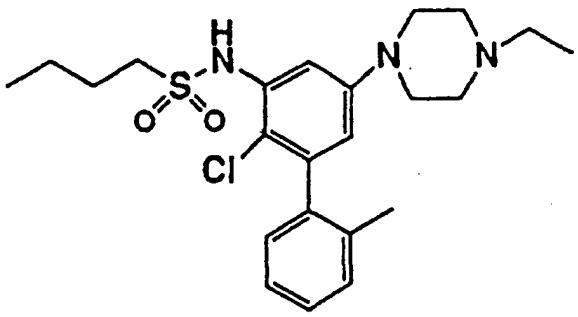


m.p.; 155°C

^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7-7.2(4H, m), 7.1(1H, d), 6.6(1H, m), 3.7(2H, q), 3.3(4H, m), 2.4(2H, q), 2.1(3H, s), 1.4(3H, t), 1.2(3H, t), 1.1(3H, t).

Example 19 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-butanesulfonylamino]phenylpiperazine

[0087]



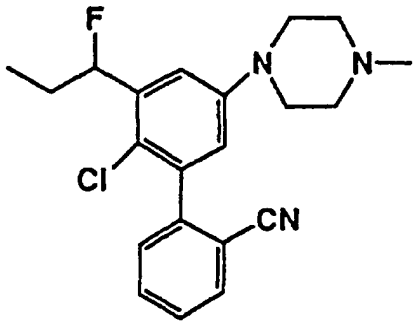
m.p.; 175°C

^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7-7.2(4H, m), 7.1(1H, d), 6.6(1H, d), 3.2(4H, m), 3.1(2H, m), 2.6(4H, m), 2.5(2H, q), 2.1(3H, s), 1.8(2H, m), 1.4(2H, m), 1.1(3H, t), 0.9(3H, t).

[0088] The following compounds were prepared as colorless oils in yields of 85 and 90% respectively in a similar manner to that of the Example 13 except that the 2-bromoethanol was replaced by methyl iodide or ethyl iodide.

Example 20 1-Methyl-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

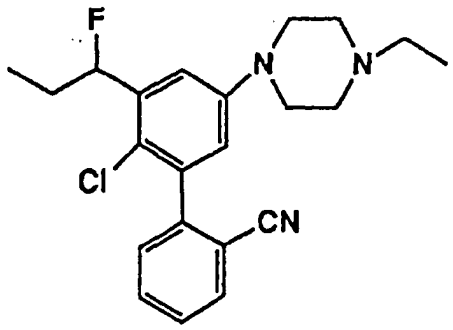
[0089]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.8(1H, d), 7.65(1H, t), 7.5(1H, t), 7.4(1H, d), 7.1(1H, d), 6.8(1H, d), 5.8(1H, m), 3.2 (4H, m), 2.6(4H, m), 2.4(3H, s), 2.0(2H, m), 1.1(3H, t).

Example 21 1-Ethyl-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

[0090]

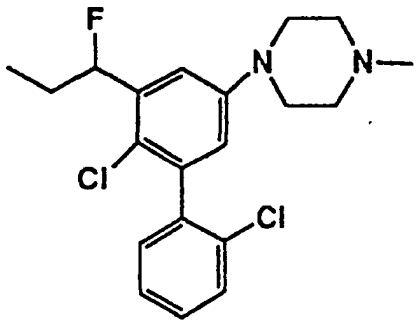


^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.8(1H, d), 7.6(1H, t), 7.5(1H, t), 7.0(1H, d), 7.1(1H, d), 6.8(1H, d), 5.8(1H, m), 3.3 (4H, m), 2.6(4H, m), 2.5(2H, q), 2.0(3H, m), 1.2(3H, t), 1.1(3H, t).

[0091] The following compounds were prepared by effecting the process described in Example 9 except that the 2-(1,3,2)-dioxaborinan-2-yl)benzaldehyde was replaced by 2-chlorophenyl-1,3,2-dioxaborinane, and subsequently effecting the process described in Examples 12 or 13.

Example 22 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

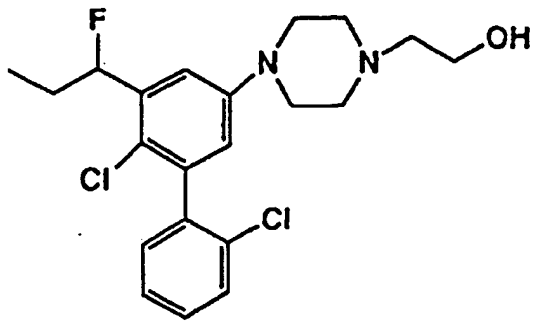
[0092]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(1H, m), 7.3(2H, m), 7.2(1H, m), 7.1(1H, d), 6.8(1H, s), 5.8(1H, m), 3.2(4H, m), 2.3(3H, s), 2.0(3H, m), 1.0(3H, t).

Example 23 1-(2-Hydroxyethyl)-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

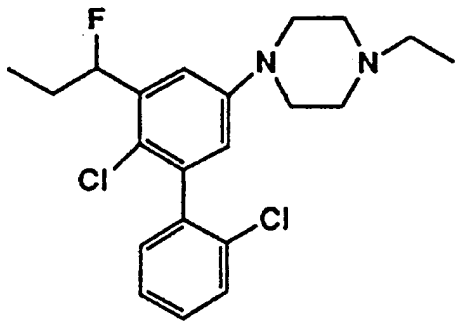
[0093]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(1H, m), 7.3(2H, m), 7.2(1H, m), 7.05(1H, d), 6.8(1H, d), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 2.0(2H, m), 1.2(3H, t), 1.1(3H, d-t).

Example 24 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

[0094]

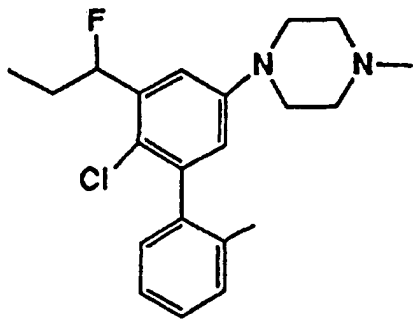


^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5-7.2 (4H, m), 7.1(1H, d), 6.8(1H, m), 5.8(1H, m), 3.7(4H, m), 3.2(4H, m), 2.7(4H, m), 2.6(2H, m), 2.0(2H, m), 1.6(1H, b-s), 1.1(3H, d-t).

[0095] The following compounds were prepared in a similar manner to that of the Example 9 except that the 2-(1,3,2-dioxaborinan-2-yl)benzaldehyde was replaced by 2-tolyl-1,3,2-dioxaborinane.

Example 25 1-Methyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

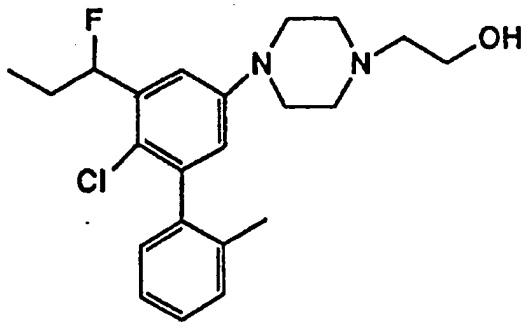
[0096]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.2 (3H, m), 7.1(1H, m), 7.0(1H, d), 6.7(1H, d), 6.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.3(3H, s), 2.1(3H, d), 1.9(2H, m), 1.1(3H, m).

Example 26 1-(2-Hydroxyethyl)-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

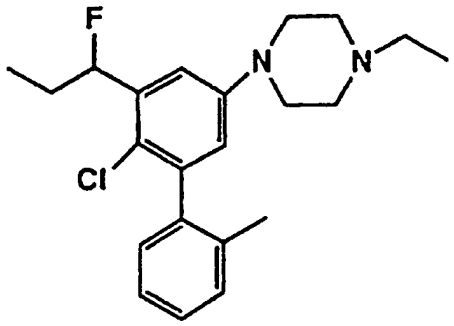
[0097]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.2 (3H, m), 7.1(1H, m), 7.0(1H, d), 6.7(1H, d), 5.8(1H, m), 3.7(2H, t), 3.2(4H, m), 2.7(2H, t), 2.6(2H, t), 2.1(3H, d), 1.9(2H, m), 1.1(3H, m).

Example 27 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

[0098]

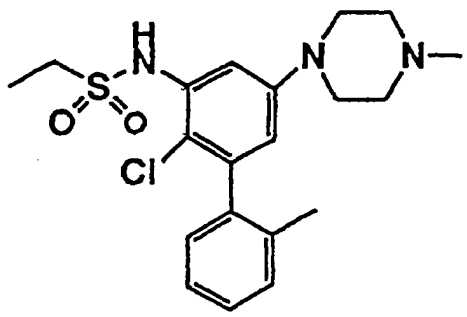


^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.2 (3H, m), 7.1(1H, m), 7.0(1H, d), 6.7(1H, d), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 2.1(3H, d), 1.9(2H, m), 1.15(3H, t), 1.05(3H, m).

[0099] The following compounds were prepared first in the same manner as that of the Example 14 except that the ethyl bromide was replaced by methyl iodide, then in the same manner as that of the Example 15 wherein the 2-tolylboric acid was used or replaced by 2-chloroboric acid.

Example 28 1-Methyl-4-[3-(2-tolyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine

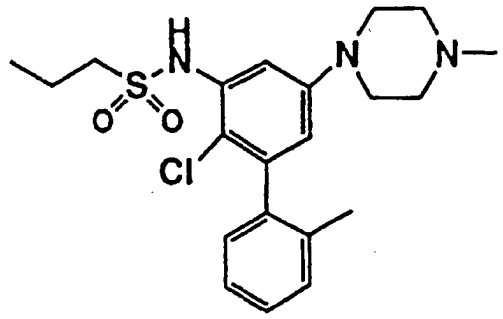
[0100]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3(4H, m), 7.1(1H, d), 6.6(1H, d), 3.3(4H, m), 3.2(2H, q), 2.6(4H, m), 2.4(3H, s), 2.1(3H, s), 1.4(3H, t).

Example 29 1-Methyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine

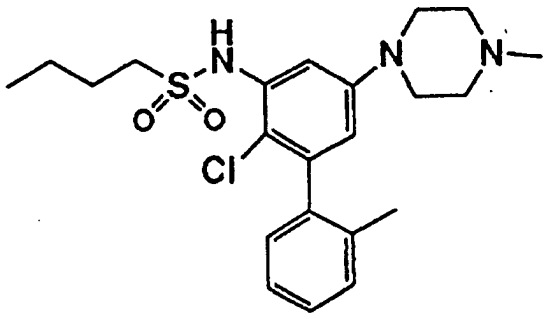
[0101]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(1H, m), 7.4-7.2(4H, m), 6.5(1H, m), 3.2(4H, m), 2.6(4H, m), 2.4(3H, s), 1.2(3H, m).

Example 30 1-Methyl-4-[3-(2-tolyl)-4-chloro-5-butanesulfonylamino]pheny]piperazine

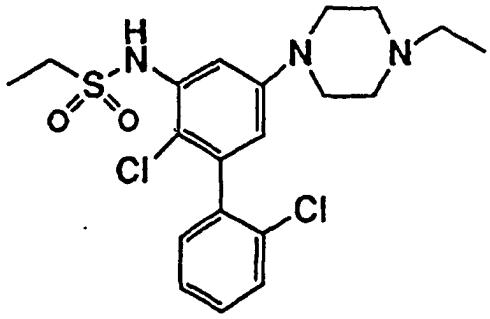
[0102]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3(4H, m), 7.1(1H, d), 6.6(1H, m), 3.2(4H, m), 3.1(2H, m), 2.6(4H, m), 2.3(3H, s), 2.1(3H, s), 1.8(2H, m), 1.4(2H, m), 0.9(3H, t).

Example 31 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine

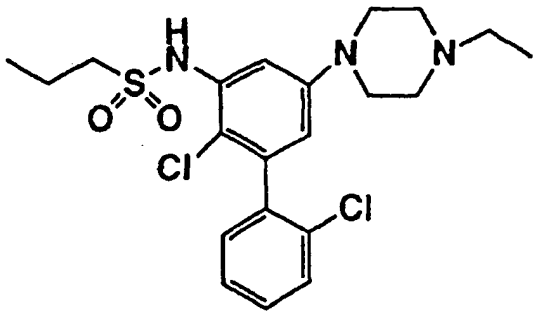
[0103]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7(2H, m), 7.2-7.5(4H, m), 6.6(1H, d), 3.3(4H, m), 3.1(2H, q), 2.6(4H, m), 2.5(2H, q), 1.4(3H, t), 1.1(3H, t).

Example 32 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine

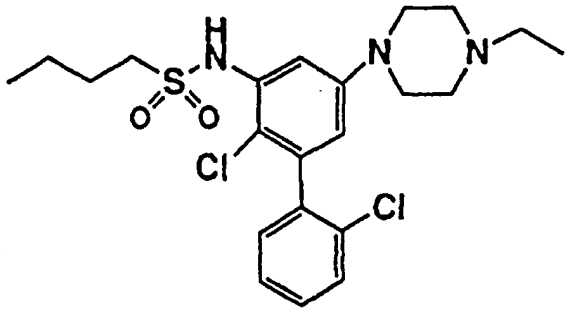
[0104]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(1H, m), 7.4(2H, m). 7.3(1H, m), 7.0(1H, d), 6.8(1H, d), 3.8(2H, m), 3.6(4H, m), 3.2(2H, m), 3.1(4H, m), 1.7(2H, q), 1.2(3H, t), 0.9(3H, t).

Example 33 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-butanesulfonylamino]phenylpiperazine

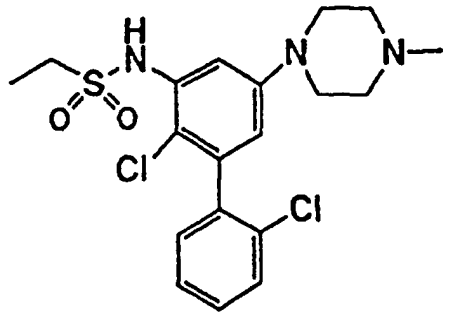
[0105]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7-7.2(5H, m), 6.6(1H, m), 3.2(4H, m), 3.1(2H, m), 2.6(4H, m), 2.5(2H, q), 1.8(2H, m), 1.4(2H, m), 1.1(3H, t), 0.9(3H, t).

Example 34 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine

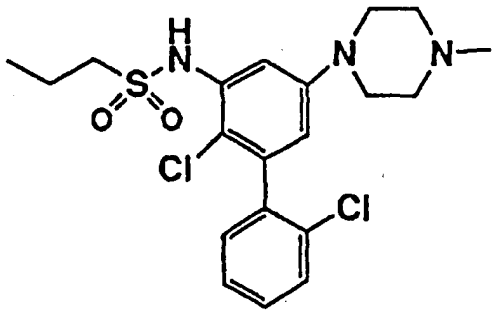
[0106]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(1H, m), 7.4-7.2(4H, m), 6.8(1H, b-s), 6.6(1H, d), 3.25(4H, m), 3.2(2H, q), 2.6 (4H, m), 2.4(3H, s), 1.4(3H, t).

Example 35 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine

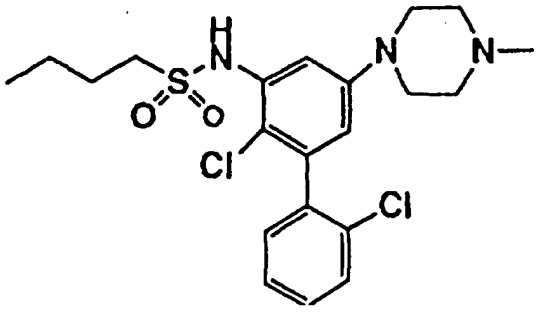
[0107]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(1H, m), 7.4-7.2(4H, m), 6.6(1H, d), 3.2(4H, m), 3.1(2H, m), 2.6(4H, m), 2.4(3H, s), 1.2(3H, m), 1.0(3H, t).

Example 36 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-butanesulfonylamino]phenylpiperazine

[0108]

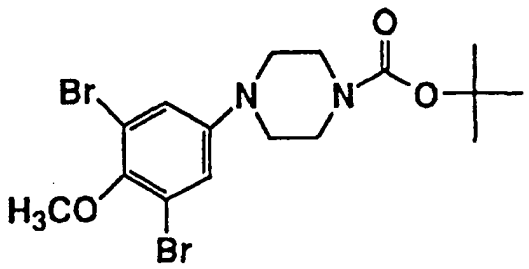


^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(1H, m), 7.4-7.2(4H, m), 6.6(1H, m), 3.2(4H, m), 3.1(2H, m), 2.6(4H, m), 2.4(3H,

s), 1.8(2H, m), 1.4(2H, m), 0.9(3H, t).

Example 37 Synthesis of 1-(t-butoxycarbonyl)-4-(3,5-dibromo-4-methoxy)phenylpiperazine

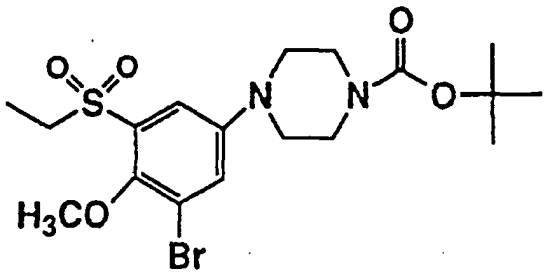
[0109]



[0110] 440 g of the title compound was prepared from 350 g of 1-(3,5-dibromo-4-methoxy)phenylpiperazine in a similar manner to that of the Example 6.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.0(2H, m), 3.8(3H, s), 3.5(4H, m), 3.0(4H, m), 1.2(9H, s).

Example 38 Synthesis of 1-(t-butoxycarbonyl)-4-(3-bromo-4-methoxy-5-ethanesulfonyl)phenylpiperazine

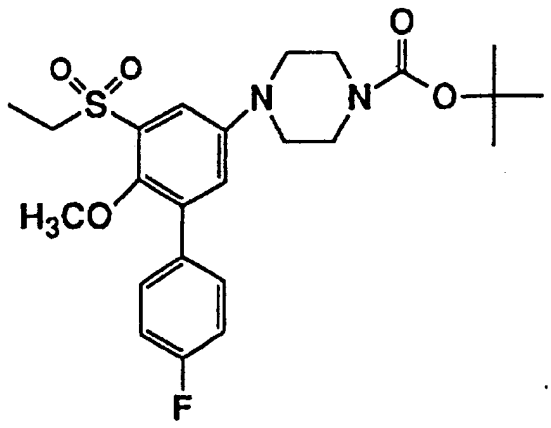
[0111]



[0112] 440 g (0.97 mol) of 1-(t-butoxycarbonyl)-4-(3,5-dibromo-4-methoxy)phenylpiperazine was dissolved in 2000 ml of THF, followed by the dropwise addition of 1.2 equivalents of n-butyllithium at -78°C. The obtained mixture was as such stirred for 30 minutes. Sulfur dioxide gas was blown into the resulting mixture for one hour, followed by the addition of 1.2 equivalents of ethyl iodide. The mixture was brought to a room temperature and then partitioned between water and ethyl acetate. The organic phase was washed with water, dried and concentrated under reduced pressure to give 250 g of the title compound.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4(1H, m), 7.3(1H, m), 4.0(3H, s), 3.6(4H, m), 3.4(2H, q), 3.2(4H, m), 1.5(9H, s), 1.2(3H, t).

Example 39 Synthesis of 1-(t-butoxycarbonyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine

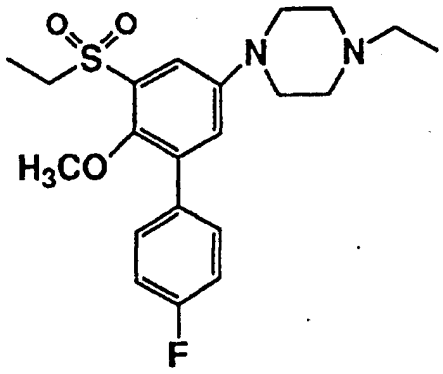
[0113]



[0114] 250 g of the title compound was prepared from 440 g of 1-(t-butoxycarbonyl)-4-(3-bromo-4-methoxy-5-ethanesulfonyl)phenylpiperazine in a similar manner to that of the Example 9.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4(1H, m), 7.2(2H, m), 7.0(1H, m), 3.6(4H, m), 3.5(2H, q), 3.4(3H, s), 3.2(4H, m), 1.5(9H, s), 1.3(3H, t).

Example 40 Synthesis of 1-ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine

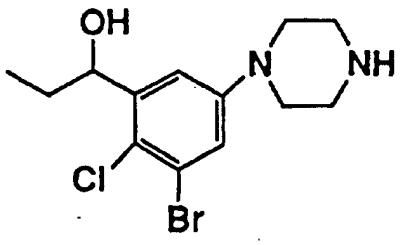
[0115]



[0116] 180 g of the title compound was prepared from 250 g of 1-(t-butoxycarbonyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine in a similar manner to that of the Example 12 or 13.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4(1H, m), 7.2(2H, m), 7.05(1H, m), 3.5(2H, q), 3.4(3H, s), 3.3(4H, m), 2.6(4H, m), 2.5(2H, q), 1.3(3H, t), 1.1(3H, t).

Example 41 Synthesis of 1-[3-bromo-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine

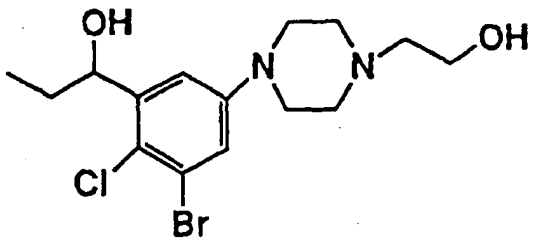
[0117]



[0118] 41.7 g (0.1 mol) 1-(t-butoxycarbonyl)-4-[3-bromo-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine was dissolved in 100 ml of 10% hydrochloric acid/ethanol. The obtained solution was stirred at room temperature one whole day and night and then distilled to remove the solvent. The obtained residue was partitioned between ethyl acetate and a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was dehydrated and distilled to remove the solvent, giving 30 g of the title compound as a colorless oil (in a yield of 95%).
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1(2H, m), 5.0(1H, m), 3.3(4H, m), 3.1(4H, m), 1.7(2H, m), 1.0(3H, t).

Example 42 Synthesis of 1-(2-hydroxyethyl)-4-[3-bromo-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine

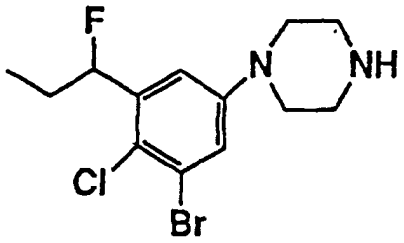
[0119]



[0120] 30 g (0.095 mol) of 1-[3-bromo-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine was dissolved in 100 ml of dry DMF, followed by the addition of 20 g of potassium carbonate and 12.5 g (0.1 mol) of bromoethanol. The obtained mixture was stirred at 50°C one whole day and night and then partitioned between ethyl acetate and water. The organic phase was dehydrated and concentrated under reduced pressure. The residue was purified by column chromatography (with methylene chloride/methanol) to give 17.1 g of the title compound as a colorless oil (in a yield of 50%).
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1(2H, m), 5,0(1H, m), 3.6(2H, m), 3.2(4H, m), 2.7(4H, m), 2.6(2H, m), 1.7(2H, m), 1.0(3H, t).

Example 43 Synthesis of 1-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

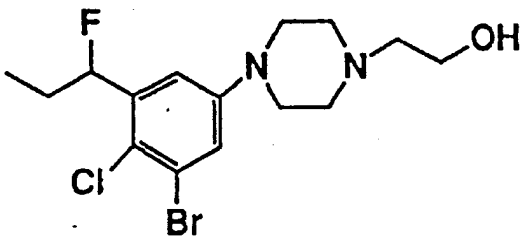
[0121]



[0122] 38 g (0.09 mol) of 1-(t-butoxycarbonyl)-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine prepared in Example 8 was dissolved in 10% hydrochloric acid/ethanol. The obtained solution was stirred at room temperature one whole day and night and then distilled to remove the solvent. The residue was partitioned between ethyl acetate and a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was dehydrated and distilled to remove the solvent, giving 28.9 g of the title compound as a colorless oil (in a yield of 100%).
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1(1H, d), 7.0(1H, d), 5.7(1H, m), 3.2(4H, m), 3.1(4H, m), 1.9(2H, m), 1.0(3H, t).

Example 44 Synthesis of 1-(2-hydroxyethyl)-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

[0123]

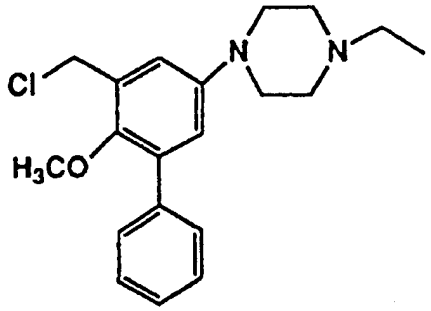


[0124] 28.9 g (0.09 mol) of 1-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine was dissolved in 50 ml of dry DMF, followed by the addition of 18.6 g (0.135 mol) of potassium carbonate and 12.5 g (0.1 mol) of bromoethanol. The obtained mixture was stirred at 50°C one whole day and night. Ethyl acetate and water were added to the reaction mixture to conduct partition. The organic phase was dehydrated and concentrated under reduced pressure. The obtained residue was purified by column chromatography (with methylene chloride/methanol) to give 22.8 g of the title compound as a colorless oil (in a yield of 70%).
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1(1H, d), 7.0(1H, d), 5.7(1H, m), 3.6(2H, m), 3.2(4H, m), 2.7(4H, m), 2.6(2H, m), 1.9(2H, m), 1.0(3H, t).

[0125] The following compounds were each prepared in a similar manner to that described above.

Example 45 1-Ethyl-4-(3-phenyl-4-methoxy-5-chloromethyl)phenylpiperazine

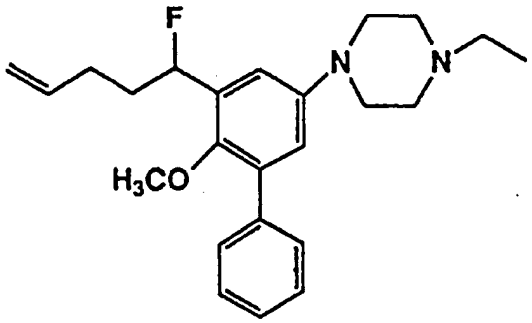
[0126]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.45(2H, m), 7.4(1H, m), 7.1(1H, m), 6.95(1H, m), 4.75(2H, s), 3.7(4H, m), 3.3(3H, s), 3.2-3.0(6H, m), 1.25(3H, t).

Example 46 1-Ethyl-4-{3-phenyl-4-methoxy-5-[1-fluoro-(4-pentenyl)]}phenylpiperazine

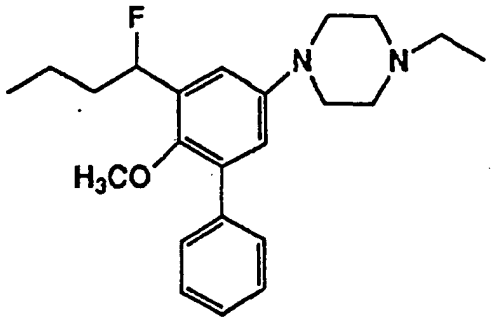
[0127]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(3H, m), 7.0(1H, s), 6.9(1H, s), 5.9(1H, m), 5.8(1H, m), 5.0(2H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 2.2(4H, m), 1.1(3H, t).
Mass; MH^+ 383

Example 47 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-fluorobutyl)]phenylpiperazine

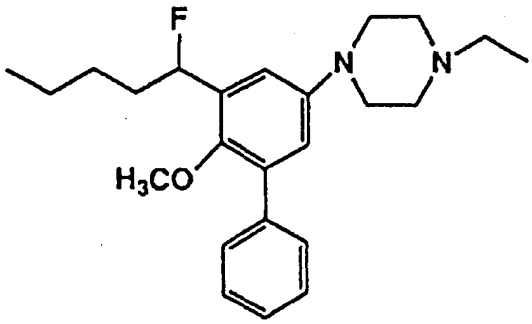
[0128]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(3H, m), 7.0(1H, d), 6.8(1H, d), 5.8(1H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.9(2H, m), 1.5(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 48 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-fluoropentyl)]phenylpiperazine.

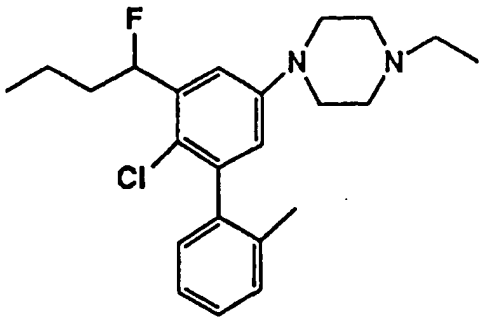
[0129]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(3H, m), 7.0(1H, d), 6.8(1H, d), 5.8(1H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 2.0(2H, m), 1.4(4H, m), 1.1(3H, t), 0.9(3H, t).

Example 49 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine

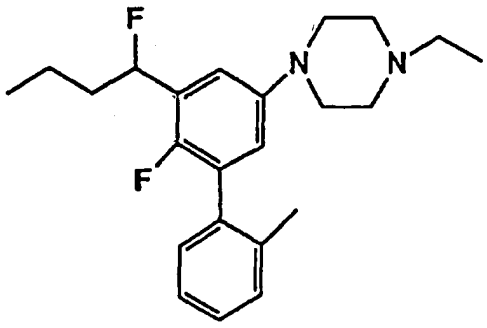
[0130]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.1(5H, m), 6.7(1H, d), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 2.1(3H, d), 1.9(2H, m), 1.6(4H, m), 1.1(3H, t), 1.0(3H, t).

Example 50 1-Ethyl-4-[3-(2-tolyl)-4-fluoro-5-(1-fluorobutyl)]phenylpiperazine

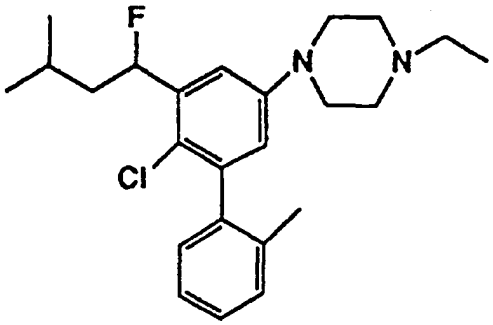
[0131]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.2(4H, m), 7.0(1H, m), 6.7(1H, m), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 2.2(3H, s), 1.8(4H, m), 1.1(3H, t), 1.0(3H, t).
Mass; MH^+ 373

Example 51 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoro-3-methylbutyl)]phenylpiperazine

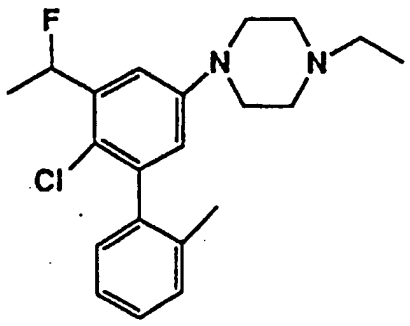
[0132]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.0(5H, m), 6.7(1H, d), 5.9(1H, m), 3.2(4H, m), 2.6(4H, m), 2.4(2H, q), 2.1(3H, m), 2.0-1.6(3H, m), 1.1(3H, m), 1.0(6H, d-t).
Mass; MH^+ 403

Example 52 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoroethyl)]phenylpiperazine

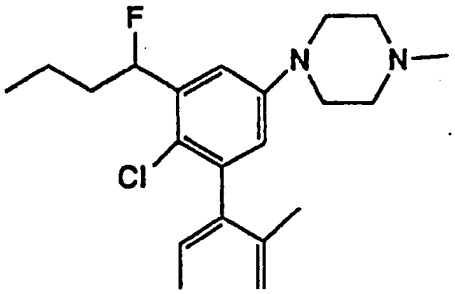
[0133]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.1(5H, m), 6.7(1H, m), 6.0(1H, m), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 2.1(3H, m), 1.6(3H, m), 1.1(3H, t).
Mass; MH^+ 361

Example 53 1-Methyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine

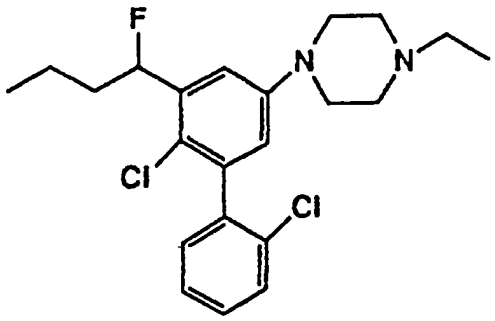
[0134]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3(3H, m), 7.1(2H, m), 6.7(1H, m), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.4(3H, s), 2.1(3H, d), 1.9(2H, m), 1.6(2H, m), 1.0(3H, m).

Example 54 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine

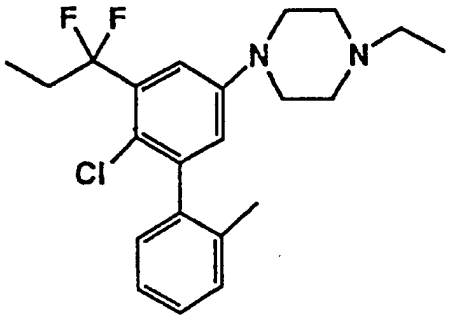
[0135]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3(4H, m), 7.1(1H, m), 6.8(1H, m), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.9(2H, m), 1.6(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 55 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1,1-difluoropropyl)]phenylpierazine

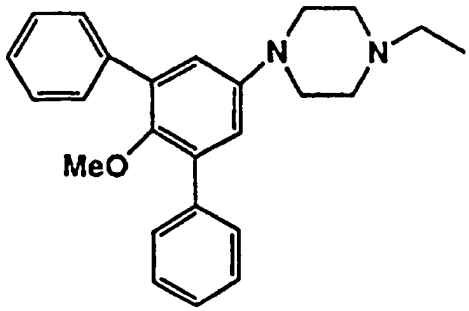
[0136]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4-7.1(5H, m), 6.8(1H, d), 3.2(4H, m), 2.6(4H, m), 2.5-2.3(4H, m), 2.1(3H, s), 1.1 (3H, t), 1.0(3H, t).

Example 56 1-Ethyl-4-(3,5-diphenyl-4-methoxy)-phenylpiperazine

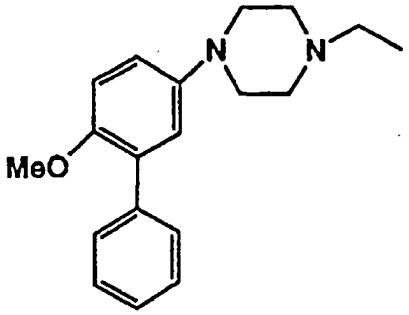
[0137]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(4H, m), 7.4(4H, m) 7.35(2H, m), 6.9(2H, s), 3.25(4H, m), 3.0(3H, s), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t).

Example 57 1-Ethyl-4-(3-phenyl-4-methoxy)phenylpiperazine

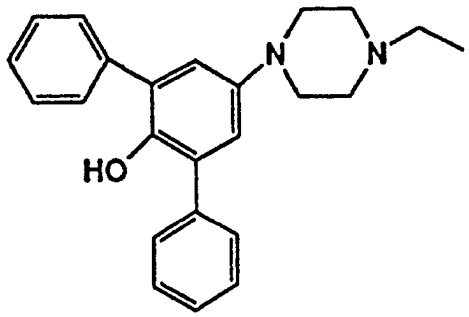
[0138]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(2H, m), 7.4(2H, m), 7.3(1H, m), 7.0(1H, m), 6.9(1H, m), 3.75(3H, s), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.1(3H, t).

Example 58 1-Ethyl-4-(3,5-diphenyl-4-hydroxy)phneylpiperazine

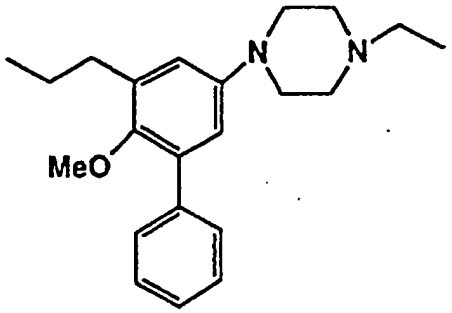
[0139]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(4H, m), 7.45(4H, m), 7.4(2H, m), 6.9(2H, s), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.1(3H, t).

Example 59 1-Ethyl-4-(3-phenyl-4-methoxy-5-propyl)-phenylpiperazine

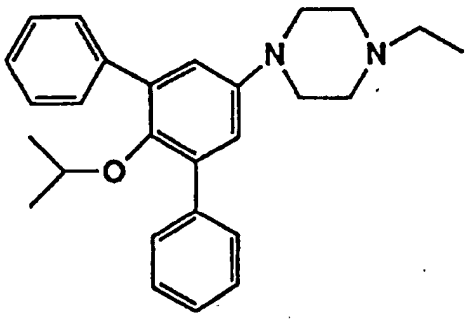
[0140]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, m), 7.3(1H, m), 6.8(2H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.6(2H, t), 2.5(2H, q), 1.6(2H, m), 1.15(3H, t), 1.0(3H, t).

Example 60 1-Ethyl-4-(3,5-diphenyl-4-isopropoxy)-phenylpiperazine

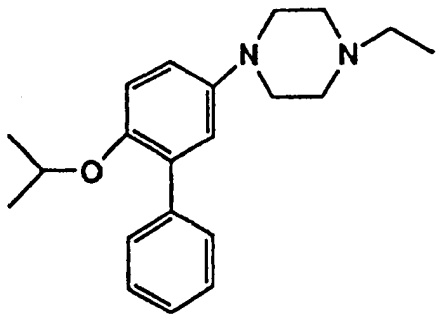
[0141]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(4H, d), 7.4(4H, m), 7.3(2H, m), 6.9(2H, s), 3.4(1H, m), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t), 1.6(6H, d).

Example 61 1-Ethyl-4-(3-phenyl-4-isopropoxy)phenylpiperazine

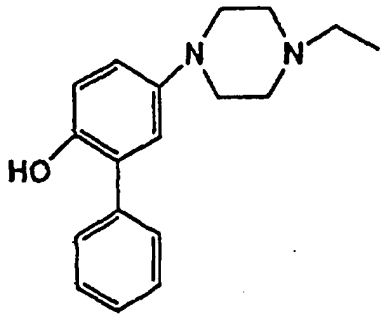
[0142]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(4H, d), 7.4(2H, m), 7.3(1H, m), 7.0-6.0(3H, m), 4.2(1H, m), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.2(3H, t).

Example 62 1-Ethyl-4-(3-phenyl-4-hydroxy)phenylpiperazine

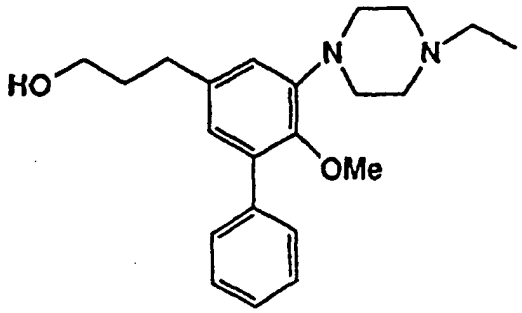
[0143]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(4H, m), 7.4(1H, m), 6.9(2H, m), 6.85(1H, m), 3.15(4H, m), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t).

Example 63 1-Ethyl-4-[2-methoxy-3-phenyl-5-(3-hydroxypropyl)]phenylpiperazine

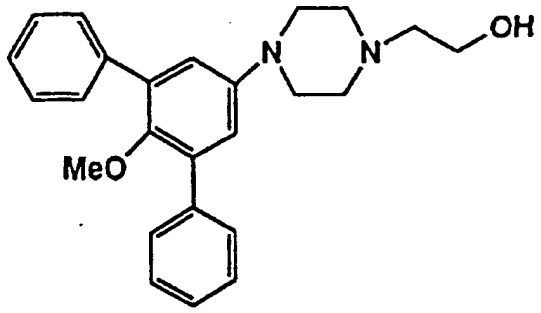
[0144]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.60(2H, d), 7.40(2H, m), 7.35(1H, m), 6.8(2H, s), 3.6(2H, t), 3.3(3H, s), 3.15(4H, m), 2.6(4H, t), 2.6(5H, m), 2.5(2H, q), 1.9(2H, m), 1.15(3H, t).

Example 64 1-(2-Hydroxyethyl)-4-(3,5-diphenyl-4-methoxy)phenylpiperazine

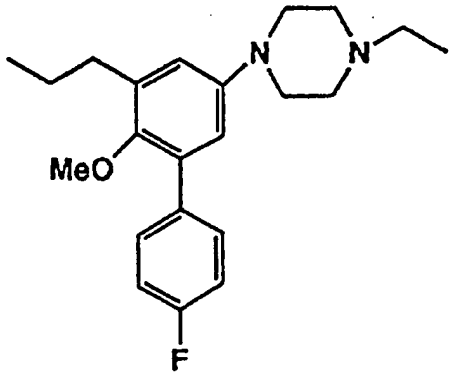
[0145]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(4H, m), 7.4(4H, m), 7.35(2H, m), 6.9(2H, s), 3.65(2H, m), 3.2(4H, m), 3.1(3H, s), 2.7(4H, m), 2.6(2H, t).

Example 65 1-Ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-propyl)]phenylpiperazine

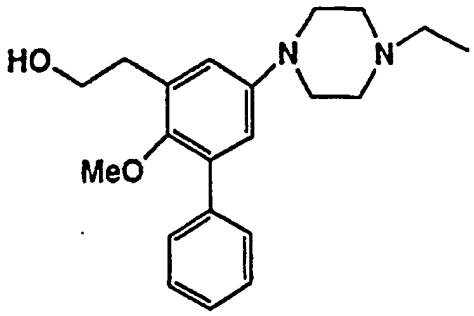
[0146]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.1(2H, m), 6.75(2H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.65(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 66 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxyethyl)]phenylpiperazine

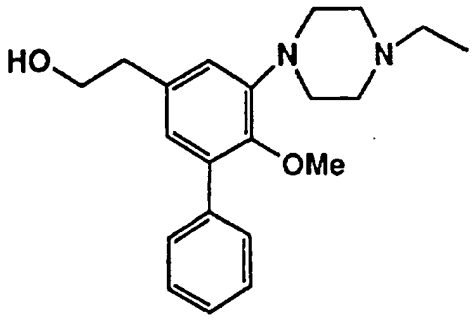
[0147]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4(2H, m 7.35(1H, m), 6.8(2H, m), 3.8(2H, t), 3.3(3H, s), 3.2(4H, m), 3.1(2H, t), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t).

Example 67 1-Ethyl-4-[2-methoxy-3-phenyl-5-(2-hydroxyethyl)]phenylpiperazine

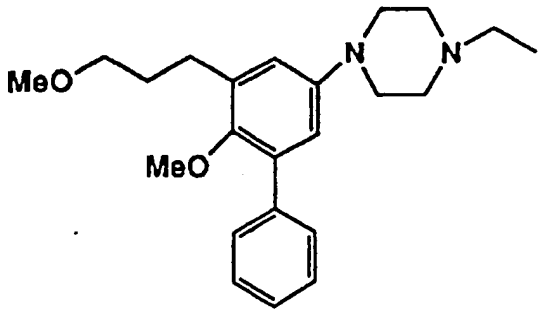
[0148]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4(2H, m), 7.35(1H, m), 6.8(2H, s), 3.9(2H, t), 3.3(3H, s), 3.2(4H, m), 2.9(2H, t), 2.6(4H, m), 2.5(2H, m), 1.1(3H, t).

Example 68 1-Ethyl-4-[3-phenyl-4-methoxy-5-(3-methoxypropyl)]phenylpiperazine

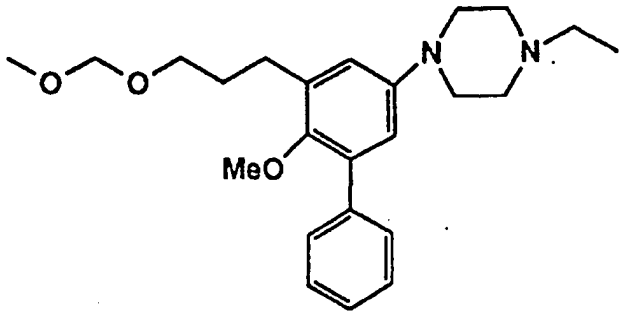
[0149]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, t), 7.3(1H, m), 6.8(2H, m), 3.45(2H, m), 3.40(3H, s), 3.30(3H, s), 3.20(4H, m), 2.7(2H, t), 2.6(4H, m), 2.5(2H, q), 1.9(2H, m), 1.1(3H, t).

Example 69 1-Ethyl-4-[3-phenyl-4-methoxy-5-(3-methoxymethoxypropyl)]phenylpiperazine

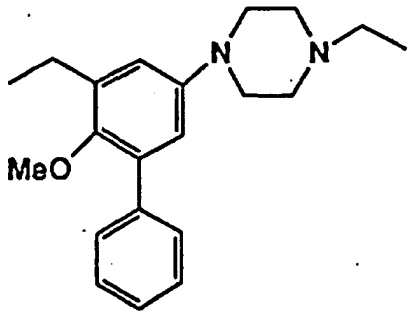
[0150]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, m), 7.35(1H, m), 6.8(2H, m), 3.6(2H, t), 3.4(3H, s), 3.3(3H, s), 3.2(4H, m), 2.8(2H, m), 2.6(4H, m), 2.5(2H, q), 2.0(2H, m), 1.1(3H, t).

Example 70 1-Ethyl-4-(3-phenyl-4-methoxy-5-ethyl)-phenylpiperazine

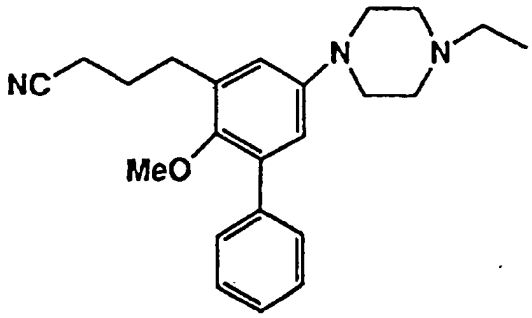
[0151]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, m), 7.35(1H, m), 6.8(2H, m), 3.3(3H, s), 3.2(4H, m), 2.7(2H, q), 2.6(4H, m), 2.5(2H, q), 1.25(3H, t), 1.1(3H, t).

Example 71 1-Ethyl-4-[3-phenyl-4-methoxy-5-(3-cyanopropyl)]phenylpiperazine

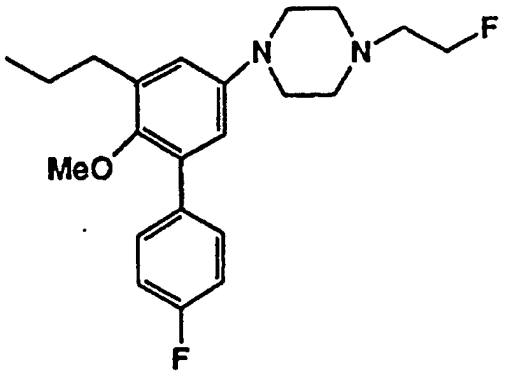
[0152]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, m), 7.35(1H, m), 6.8(2H, m), 3.3(3H, s), 3.2(4H, m), 2.8(2H, t), 2.6(4H, m), 2.5(2H, q), 2.4(2H, t), 2.0(2H, m), 1.1(3H, t).

Example 72 1-(2-Fluoroethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-propyl]phenylpiperazine

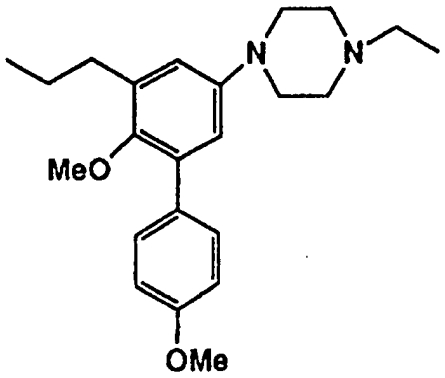
[0153]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.1(2H, m), 6.75(2H, m), 4.6(2H, d-t), 3.3(3H, s), 3.2(4H, m), 2.7(4H, m), 2.7(2H, m), 1.7(2H, m), 1.0(3H, t).

Example 73 1-Ethyl-4-[3-(4-methoxyphenyl)-4-methoxy-5-propyl]phenylpiperazine

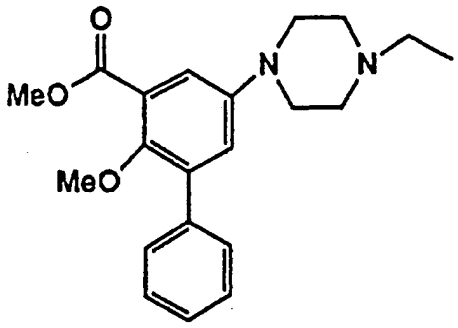
[0154]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(2H, m), 6.95(2H, m), 6.75(2H, m), 3.85(3H, s), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.7(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 74 1-Ethyl-4-(3-phenyl-4-methoxy-5-methoxycarbonyl)pheylpiperazine

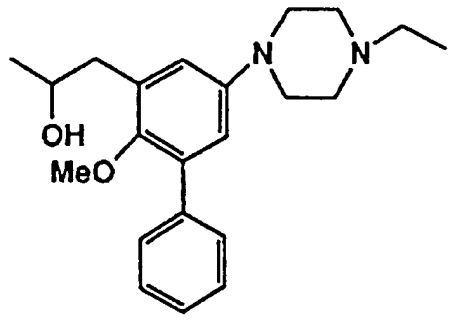
[0155]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, m), 7.3(1H, m), 7.0(1H, m), 3.95(3H, s), 3.4(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t).

Example 75 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxypropyl)]phenylpiperazine

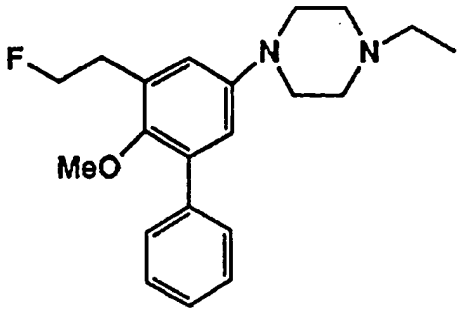
[0156]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, m), 7.35(1H, m), 6.8(2H, s), 4.1(1H, m), 3.3(3H, s), 3.2(4H, m), 3.0(1H, b-s), 2.8(2H, m), 2.6(4H, m), 2.4(2H, q), 1.25(3H, d), 1.1(3H, t).

Example 76 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-fluoroethyl)]phenylpiperazine

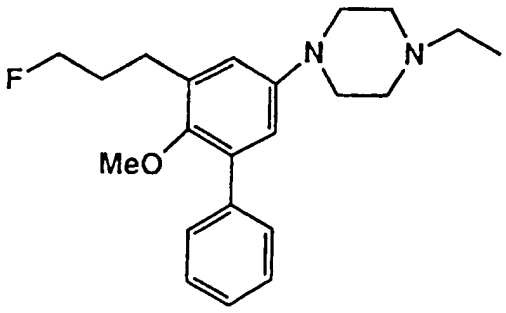
[0157]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, m 7.35(1H, m), 6.8(2H, m), 4.75(2H, t), 4.6(2H, t), 3.3(3H, s), 3.2(4H, m), 3.1(2H, t), 3.05(2H, t), 2.6(4H, m), 2.5(2H, q), 1.15(3H, t).

Example 77 1-Ethyl-4-[3-phenyl-4-methoxy-5-(3-fluoropropyl)]phenylpiperazine

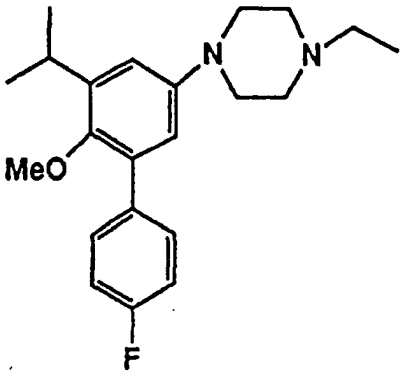
[0158]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, m), 7.35(1H, m), 6.8(2H, s), 4.6(2H, t), 4.45(2H, t), 3.3(3H, s), 3.2(4H, m), 2.8(2H, m), 2.6(4H, m), 2.5(H, q), 2.05(2H, m), 1.15(3H, t).

Example 78 1-Ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-isopropyl]phenylpiperazine

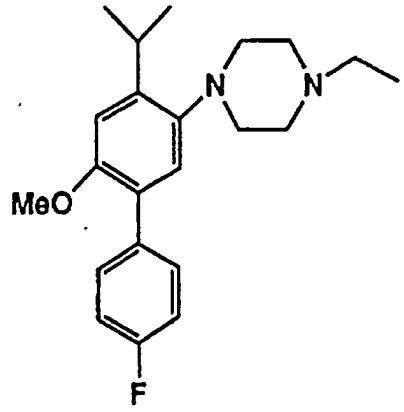
[0159]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.1(2H, m), 6.8(1H, m), 6.7(1H, m), 3.4(1H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.25(6H, s), 1.1(3H, t).

Example 79 1-Ethyl-4-[3-(4-fluorophenyl)-4-methoxy-6-isopropyl]phenylpiperazine

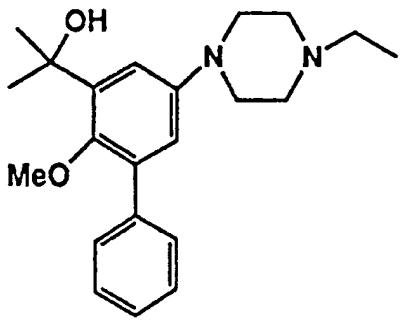
[0160]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.4(1H, m), 7.1(2H, m), 6.85(1H, m), 3.8(3H, s), 3.6(1H, m), 2.9(4H, m), 2.5(2H, q), 1.55(4H, b-s), 1.25(6H, d), 1.1(3H, t).

Example 80 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxyisopropyl)]phenylpiperazine

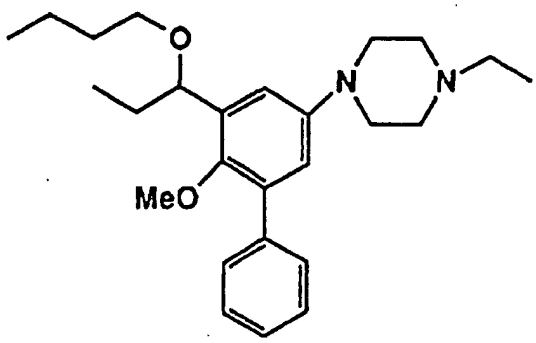
[0161]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, m), 7.35(1H, m), 6.95(1H, m), 6.98(1H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.6(6H, s), 1.1(3H, t).

Example 81 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-butoxypropyl)]phenylpiperazine

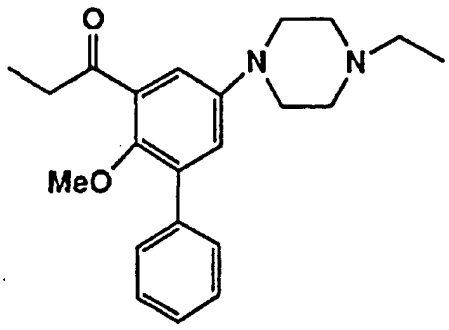
[0162]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4(2H, m), 7.35(1H, m), 7.0(1H, d), 6.8(1H, m), 4.6(1H, m), 3.4(1H, m), 3.35(1H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.75(2H, m), 1.6(2H, m), 1.4(2H, m), 1.1(3H, t), 1.0 (3H, t), 0.9(3H, t).

Example 82 1-Ethyl-4-(3-phenyl-4-methoxy-5-propionyl)phenylpiperazine

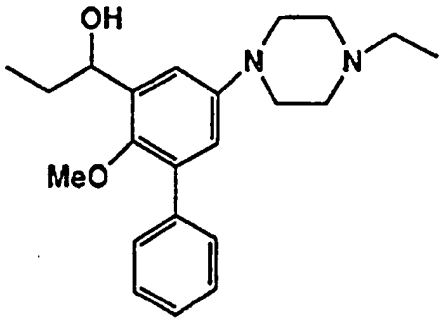
[0163]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.4(3H, m), 7.0(2H, m), 3.3(3H, s), 3.2(4H, m), 3.0(2H, q), 2.6(4H, m), 3.42(2H, q), 1.2(3H, t), 1.1(3H, t).

Example 83 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxypropyl)]phenylpiperazine

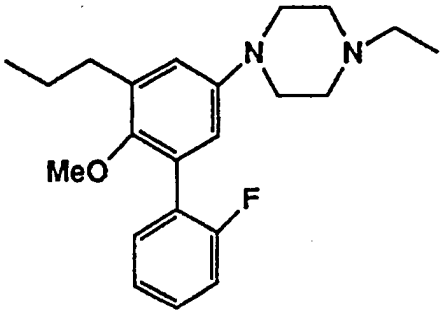
[0164]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(2H, m), 7.35(3H, m), 7.0(1H, m), 6.7(1H, m), 4.9(1H, m), 4.0(1H, b-s), 3.25(3H, s), 3.2-3.0(4H, m), 2.6(4H, m), 2.45(2H, m), 1.8(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 84 1-Ethyl-4-[3-(2-fluorophenyl)-4-methoxy-5-propyl]phenylpiperazine

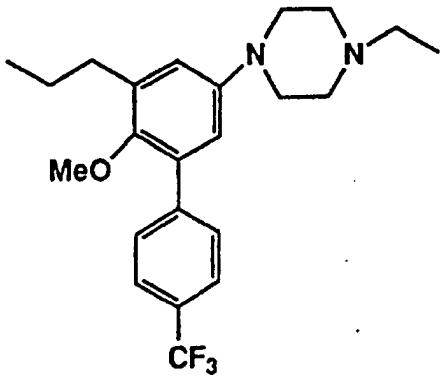
[0165]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4-7.3(2H, m), 7.2-7.1(2H, m), 6.8(1H, d), 6.7(1H, d), 3.3(3H, s), 3.2(4H, m), 2.6 (6H, m), 2.5(2H, q), 1.7(2H, m), 1.15(3H, t), 1.0(3H, t).

Example 85 1-Ethyl-4-[3-(4-trifluoromethylphenyl)-4-methoxy-5-propyl]phenylpiperazine

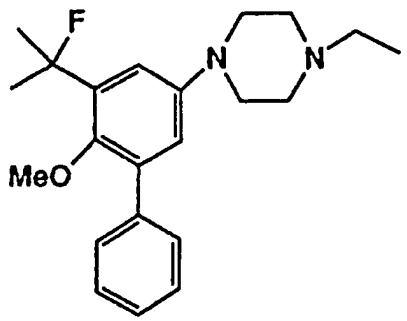
[0166]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7(4H, m), 6.8(1H, m), 6.7(1H, m), 3.3(3H, s), 3.2(4H, m), 2.6(6H, m), 2.45(2H, q), 1.7(2H, m), 1.15(3H, t), 1.0(3H, t).

Example 86 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-fluoroisopropyl)]phenylpiperazine

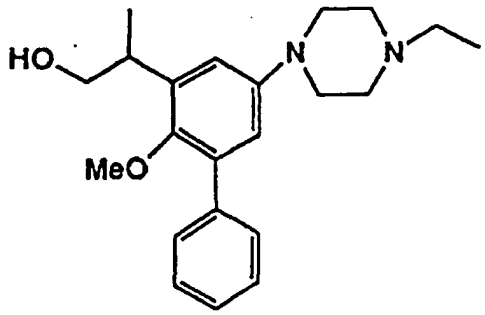
[0167]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.4(3H, m), 7.1(1H, d), 6.8(1H, d), 3.2(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.8(6H, d), 1.15(3H, t).

Example 87 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxyisopropyl)]phenylpiperazine

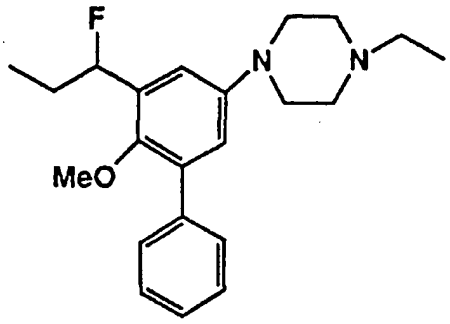
[0168]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, t), 7.35(1H, m), 6.8(2H, m), 3.75(2H, d), 3.4(1H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.95(2H, m), 1.6(2H, m), 1.3(3H, d), 1.1(3H, t).

Example 88 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-fluoropropyl)]phenylpiperazine

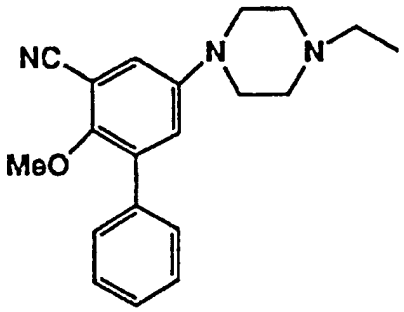
[0169]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4(3H, m), 7.0(1H, m), 6.85(1H, m), 5.75(1H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 2.0(2H, m), 1.15(3H, t), 1.05(3H, t).

Example 89 1-Ethyl-4-(3-phenyl-4-methoxy-5-cyano)-phenylpiperazine

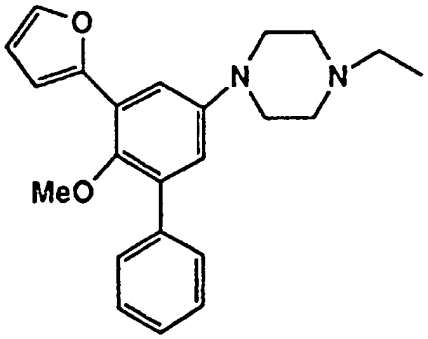
[0170]



^{1}H-NNR(400MHz, $CDCl_3$); δ(ppm) 7.5(2H, m), 7.4(3H, m), 7.1(1H, d), 7.1(1H, d), 3.6(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t).

Example 90 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-furanyl)]phenylpiperazine

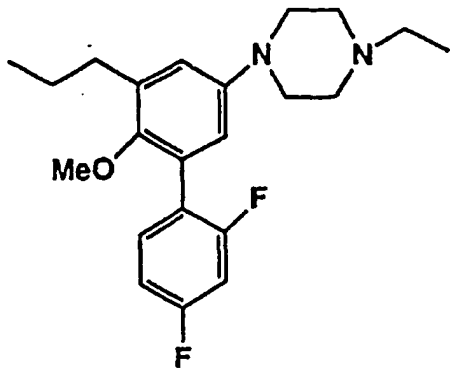
[0171]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.5-7.3(5H, m), 7.0(1H, d), 6.8(1H, d), 6.5(1H, d), 3.3(3H, s), 5.25(4H, m), 2.6(4H, m), 2.5(2H, q), 1.2(3H, t).

Example 91 1-Ethyl-4-[3-(2,4-difluorophenyl)-4-methoxy-5-propyl]phenylpiperazine

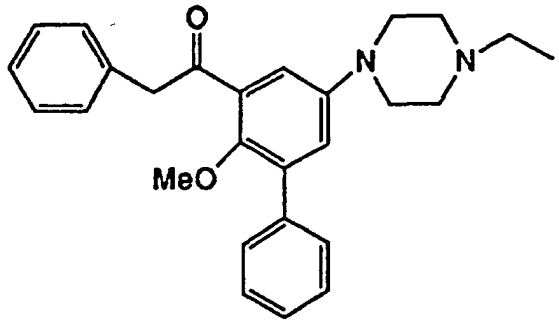
[0172]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4(1H, m), 7.0-6.9(2H, m), 6.8(1H, m), 6.65(1H, m), 3.3(3H, s), 3.2(4H, m), 2.6(6H, m), 2.5(2H, q), 1.7(2H, m), 1.15(3H, t), 1.0(3H, t).

Example 92 1-Ethyl-4-(3-phenyl-4-methoxy-5-phenylacetyl)phenylpiperazine

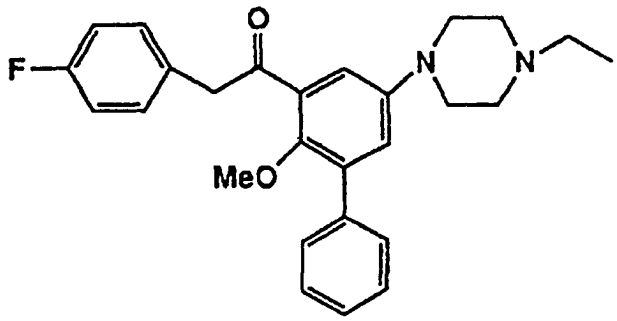
[0173]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.45-7.2(8H, m), 7.0(2H, s), 4.35(2H, s), 3.35(3H, s), 3.2(4H, m), 2.6(4H, m), 2.45(2H, m), 1.1(3H, t).

Example 93 1-Ethyl-4-[3-phenyl-4-methoxy-5-(4-fluorophenyl)acetyl]phenylpiperazine

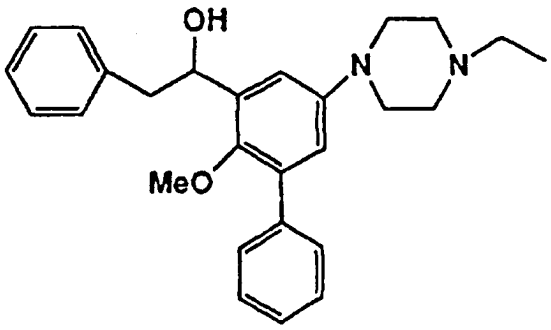
[0174]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(3H, m), 7.25(2H, m), 7.0(4H, m), 4.3(2H, s), 3.35(3H, s), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.1(3H, t).

Example 94 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxyphenethyl)]phenylpiperazine

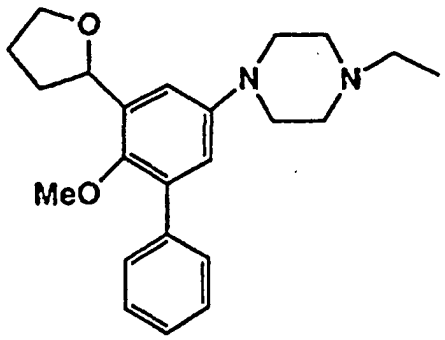
[0175]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4-7.2(8H, m), 7.0(1H, m), 6.8(1H, m), 5.2(1H, m), 3.3(3H, s), 3.2(4H, m), 3.0(1H, m), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t).

Example 95 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-tetrahydrofuranyl)]phenylpiperazine

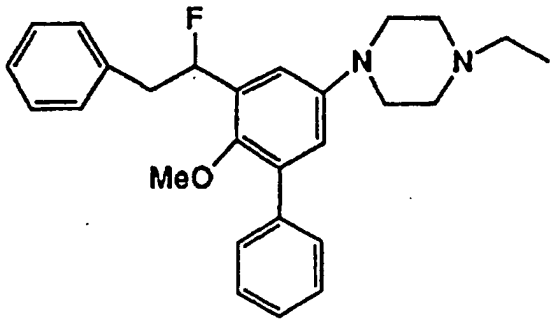
[0176]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4(2H, t), 7.35(1H, t), 7.0(1H, s), 6.8(1H, s), 5.2(1H, t), 4.1(1H, m), 3.95(1H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, m), 2.0(2H, m), 1.8(2H, m), 1.15(3H, t).

Example 96 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-fluorophenethyl)]phenylpiperazine

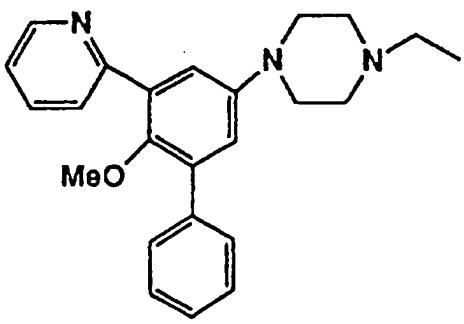
[0177]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4-7.2(8H, m), 6.95(1H, m), 6.85(1H, m), 6.0(1H, m), 3.25(3H, s), 3.2 (4H, m), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t).

Example 97 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridyl)]phenylpiperazine

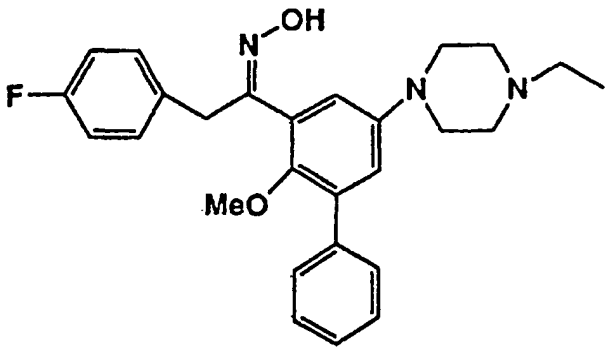
[0178]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.7(1H, m), 7.8(1H, d), 7.7(1H, t), 7.6(2H, d), 7.4(2H, t), 7.35(1H, m), 7.3(1H, d), 7.0(1H, d), 3.3(4H, m), 3.2(3H, s), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t).

Example 98 1-Ethyl-4-{3-phenyl-4-methoxy-5-[4-fluoro(1-hydroxyimino)phenethyl]}phenylpiperazine

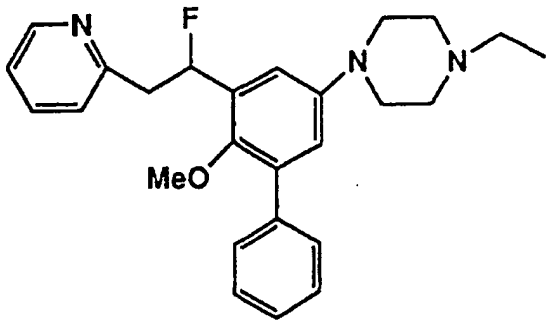
[0179]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.4(3H, m), 7.1(2H, m), 6.9(2H, m), 6.7(2H, m), 4.2(2H, s), 3.3(3H, s), 3.2(4H, m), 2.65(4H, m), 2.5(2H, m), 1.2(3H, t).

Example 99 1-Ethyl-4-{3-phenyl-4-methoxy-5-[1-fluoro-2-(2-pyridyl)ethyl]}phenylpiperazine

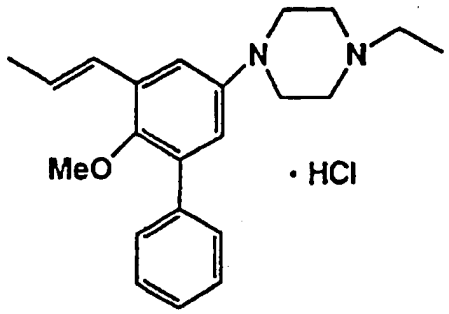
[0180]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.6(1H, m), 7.6(3H, m), 7.4(2H, m), 7.35(1H, m), 7.25(1H, m), 7.15(1H, m), 7.05 (1H, d), 6.9(1H, m), 6.25(1H, m), 3.4(2H, m), 3.3(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.15(3H, t).

Example 100 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-propenyl)]phenylpiperazine hydrochloride

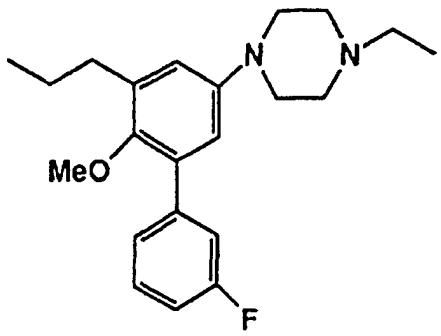
[0181]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.95(1H, m), 7.6(1H, m), 7.5(2H, m), 7.4(3H, m), 6.7(1H, d), 6.45(1H, m), 4.75(2H, t), 4.3(2H, m), 3.7(4H, m), 3.4(3H, s), 3.2(2H, m), 2.0(3H, d), 1.5(3H, t).

Example 101 1-Ethyl-4-[3-(3-fluorophenyl)-4-methoxy-5-propyl]phenylpiperazine

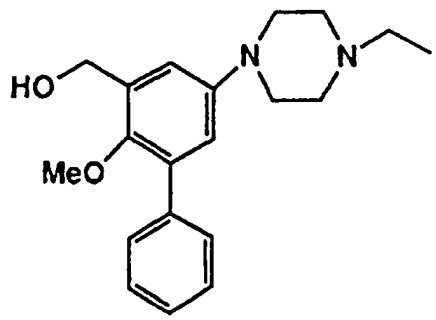
[0182]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4-7.2(3H, m), 7.0(1H, m), 6.75(2H, m), 3.3(3H, s), 3.2(4H, m), 2.6(6H, m), 2.45 (2H, q), 1.7(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 102 1-Ethyl-4-(3-phenyl-4-methoxy-5-hydroxymethyl)phenylpiperazine

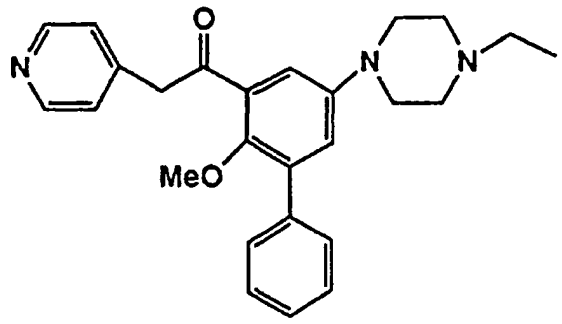
[0183]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4(3H, m), 6.9(1H, m), 6.8(1H, m), 4.7(2H, s), 3.35(3H, s), 3.2(4H, m), 2.65(4H, m), 2.5(2H, q), 1.2(3H, t).

Example 103 1-Ethyl-4-[3-phenyl-4-methoxy-5-(4-pyridyl)acetyl]phenylpiperazine

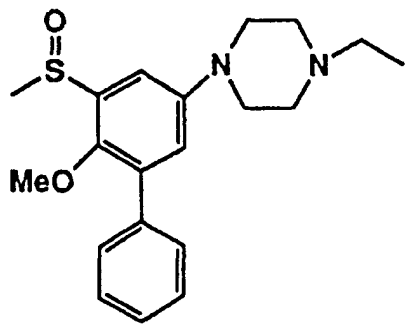
[0184]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.6(2H, m), 7.6(2H, m), 7.4(3H, m), 7.2(2H, d), 7.05(2H, m), 4.4(2H, s), 3.35(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t).

Example 104 1-Ethyl-4-(3-phenyl-4-methoxy-5-methanesulfinyl)phenylpiperazine

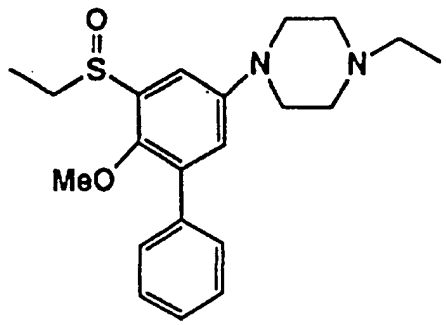
[0185]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(4H, m), 6.95(1H, d), 3.35(3H, s), 3.3(4H, m), 2.9(3H, s), 2.6(4H, m), 2.5(2H, q), 1.05(3H, t).

Example 105 1-Ethyl-4-(3-phenyl-4-methoxy-5-ethanesulfinyl)phenylpiperazine

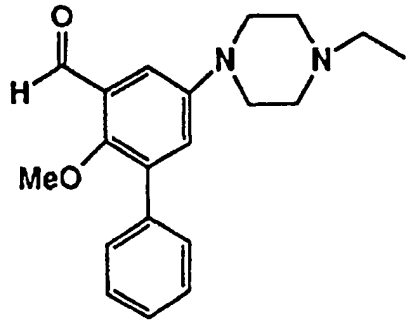
[0186]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4(3H, m), 7.3(1H, m), 6.95(1H, m), 3.35(3H, s), 3.3(4H, m), 3.15(2H, m), 2.9(2H, m), 2.6(4H, m), 2.5(2H, m), 1.3(3H, t), 1.15(3H, t).

Example 106 1-Ethyl-4-(3-phenyl-4-methoxy-5-formyl)-phenylpiperazine

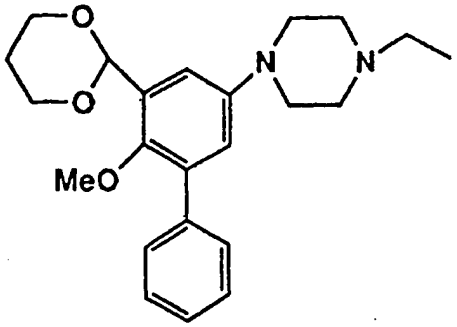
[0187]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 10.43(1H, s), 7.34-7.6(5H, m), 7.17(2H, m), 3.46(3H, s), 3.40(4H, m), 2.81(4H, m), 2.66(2H, q), 1.25(3H, t).

Example 107 1-Ethyl-4-[3-phenyl]-4-methoxy-5-(1,3-dioxan-2-yl)]phenylpiperazine

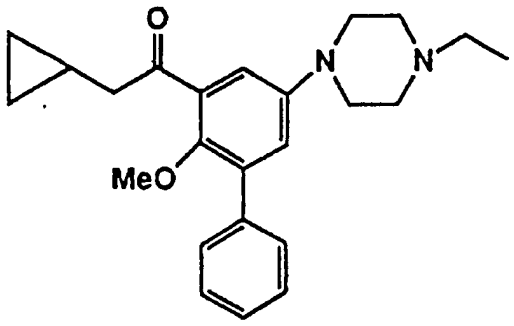
[0188]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.54(5H, m), 7.18(1H, d), 6.89(1H, d), 5.85(1H, s), 4.26(2H, d-d), 4.04(2H, d-t), 3.34(3H, s), 3.25(4H, m), 2.62(4H, m), 2.51 (2H, q), 2.25(1H, m), 1.45(1H, m), 1.15(3H, t).

Example 108 1-Ethyl-4-(3-phenyl-4-methoxy-5-cyclopropaneacetyl)phenylpiperazine

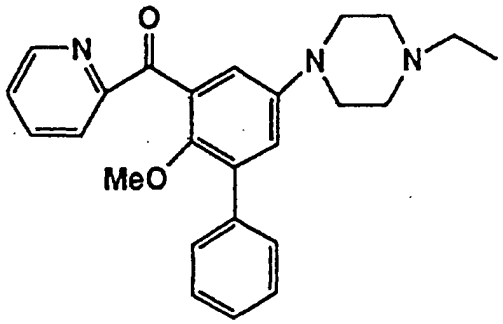
[0189]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(3H, m), 7.0(2H, m), 5.9(1H, m), 5.1(2H, m), 3.35(3H, s), 3.2(4H, m), 3.15(2H, t), 2.6(4H, m), 2.45(4H, m), 1.1(3H, t).

Example 109 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridylcarbonyl)]phenylpiperazine

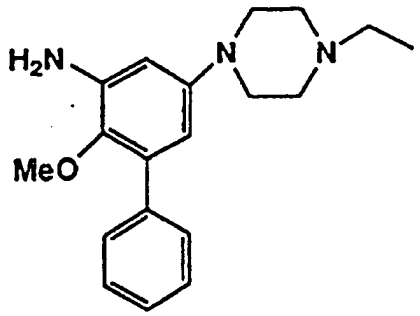
[0190]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.7(1H, m), 8.05(1H, d), 7.85(1H, m), 7.6(2H, m), 7.4(3H, m), 7.35(1H, m), 7.05 (1H, m), 7.0(1H, m), 3.2(4H, m), 3.1(3H, s), 2.66(4H, m), 2.5(2H, q), 1.1(3H, t).

Example 110 1-Ethyl-4-(3-phenyl-4-methoxy-5-amino)-phenylpiperazine

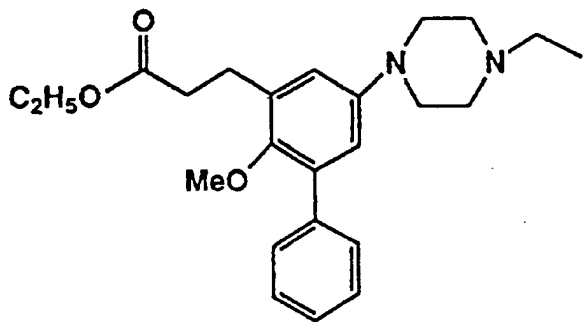
[0191]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4-7.3(3H, m), 6.35(1H, m), 6.3(1H, m), 3.9(2H, b-s), 3.7(2H, q), 3.35 (3H, s), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.2(3H, t), 1.1(3H, t).

Example 111 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-ethoxycarbonylethyl)]phenylpiperazine

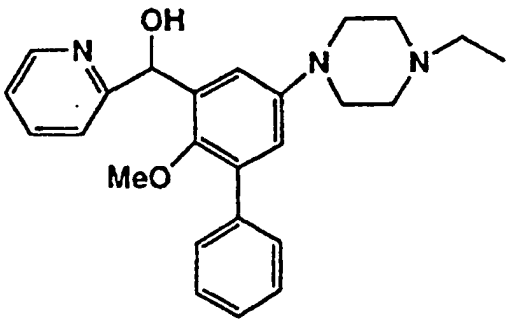
[0192]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.59(5H, m), 6.78(2H, m), 4.14(2H, q), 3.30(3H, s), 3.21(4H, m), 2.97(2H, t), 2.65(2H, t), 2.62(4H, m), 2.50(2H, q), 1.25(3H, t), 1.14(3H, t).

Example 112 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridyl)hydroxymethyl]phenylpiperazine

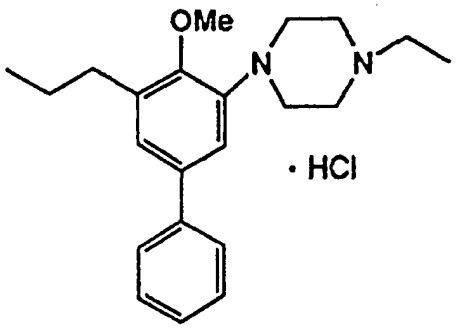
[0193]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.6(1H, m), 7.65(1H, t), 7.6(2H, m), 7.4(3H, m), 7.35(1H, m), 7.2(1H, m), 6.9(1H, m), 6.8(1H, m), 3.3(3H, s), 3.2(4H, m), 2.55(4H, m), 2.4(2H, q), 1.1(3H, t).

Example 113 1-Ethyl-4-(3-phenyl-5-propyl-6-methoxy)-phenylpiperazine hydrochloride

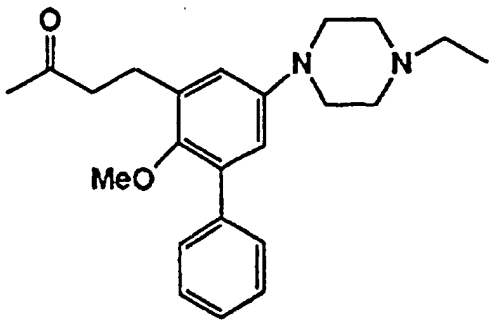
[0194]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 13.5(1H, b-s), 8.05(1H, m), 7.6(2H, m), 7.5(1H, s), 7.45(2H, t), 7.4(1H, t), 4.8(2H, m), 4.4(2H, b-s), 4.2(3H, s), 3.8(2H, d), 3.6(2H, d), 3.25(2H, b-s), 2.8(2H, t), 1.75(2H, m), 1.6(3H, b-s), 1.0(3H, t).

Example 114 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-acetylethyl)]phenylpiperazine

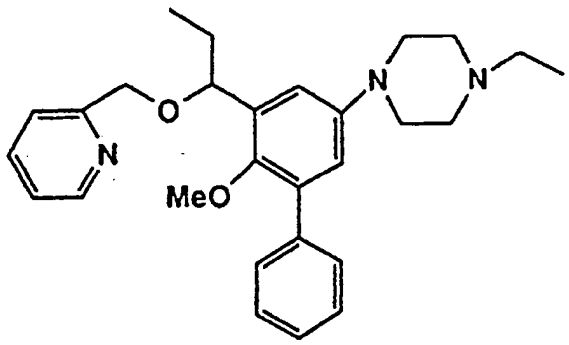
[0195]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.30-7.59(5H, m), 6.75(2H, s), 3.28(3H, s), 3.19(4H, m), 2.89(2H, m), 2.82(2H, m), 2.61(4H, m), 2.47(2H, q), 2.17(3H, s), 1.12(3H, t).

Example 115 1-Ethyl-4-{3-phenyl-4-methoxy-5-[1-(2-pyridylmethoxy)propyl]}phenylpiperazine

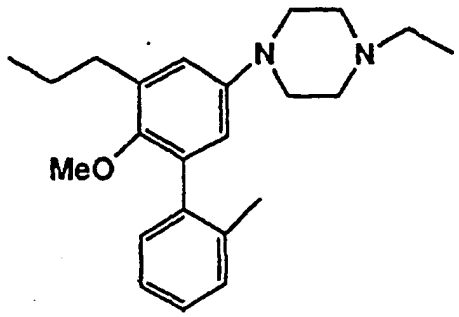
[0196]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.7(1H, d), 8.2(1H, t), 7.85(1H, d), 7.6(1H, t), 7.5(2H, m), 7.4(1H, m), 7.35(1H, m), 7.1(1H, s), 6.8(1H, s), 4.8(3H, m), 3.6(6H, m), 3.25(3H, s), 3.15(2H, q), 3.0(2H, m), 1.9(2H, m), 1.5(3H, t), 1.0(3H, t).

Example 116 1-Ethyl-4-[3-(2-tolyl)-4-methoxy-5-propyl]phenylpiperazine

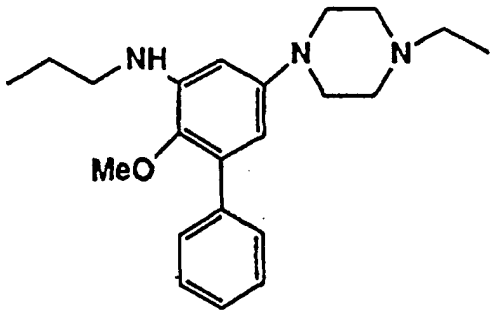
[0197]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.18-7.25(4H, m), 6.78(1H, d), 6.59(1H, d), 3.24(3H, s), 3.18(4H, m), 2.58-2.62(6H, m), 2.48(2H, q), 2.19(3H, s), 1.66(2H, m), 1.13(3H, t), 0.99(3H, t).

Example 117 1-Ethyl-4-(3-phenyl-4-methoxy-5-propylamino)phenylpiperazine

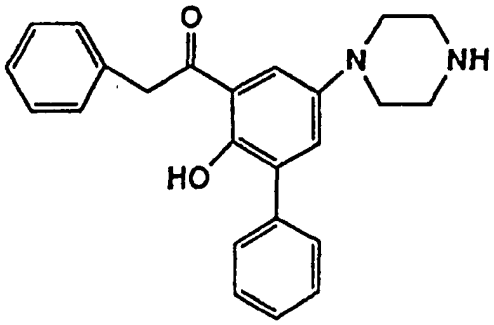
[0198]



^{1}H-NMR(400MHz, $CDCl_3$) ; δ(ppm) 7.6(2H, m), 7.4(2H, t), 7.3(1H, m), 6.25(1H, d), 6.2(1H, d), 4.3(1H, b-s), 3.3(3H, s), 3.2(4H, m), 3.1(2H, t), 2.6(4H, m), 2.5(2H, q), 1.7(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 118 1-(3-Phenyl-4-hydroxy-5-phenylacetyl)-phenylpiperazine

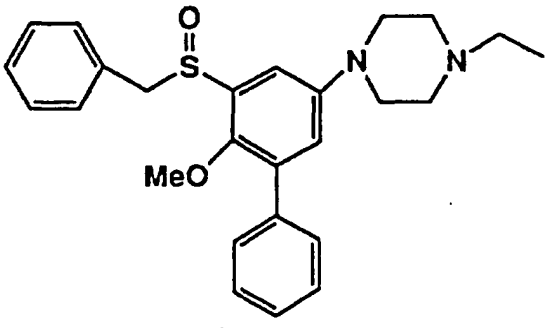
[0199]



^{1}H-NMR (400MHz, $CDCl_3$); δ(ppm) 7.55(2H, d), 7.4-7.25(5H, m), 4.35(2H, s), 3.2(8H, m).

Example 119 1-Ethyl-4-(3-phenyl-4-methoxy-5-benzylsulfinyl)phenylpiperazine

[0200]

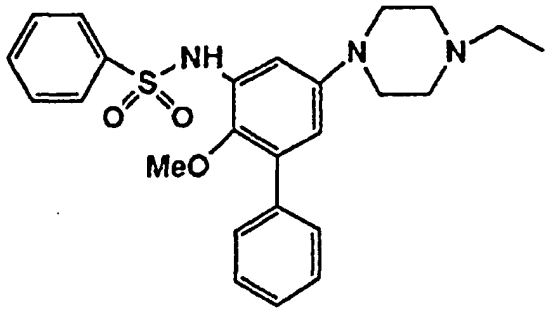


^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.5-7.35(4H, m), 7.25(2H, m), 7.1(2H, m), 6.9(2H, m), 4.2(2H, q), 3.4

(3H, s), 3.2(4H, m), 2.55(4H, m), 2.45(2H, q), 1.1(3H, t).

Example 120 1-Ethyl-4-(3-phenyl-4-methoxy-5-benzenesulfonylamino)phenylpiperazine

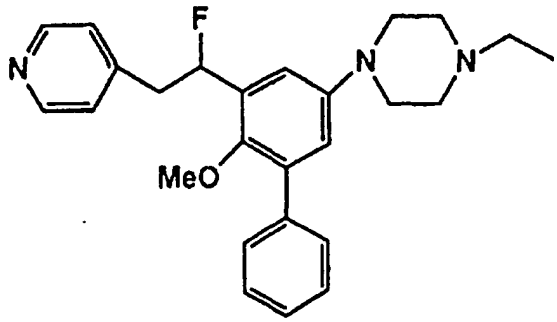
[0201]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.8(2H, m), 7.6-7.3(8H, m), 7.2(1H, d), 6.6(1H, d), 3.2(4H, m), 2.9(3H, s), 2.6(4H, m), 2.5(2H, q), 1.55(3H, t).

Example 121 1-Ethyl-4-{3-phenyl-4-methoxy-5-[1-fluoro-2-(4-pyridyl)ethyl]}phenylpiperazine

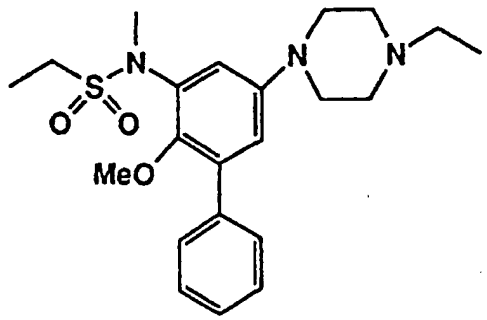
[0202]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.5(2H, d), 7.6(2H, m), 7.4(2H, m), 7.35(1H, m), 7.2(2H, d), 6.85(2H, m), 5.95(1H, m), 3.2(3H, s), 3.15(4H, m), 2.6(4H, m), 2.4(2H, q), 1.1(3H, t).

Example 122 1-Ethyl-4-[3-phenyl-4-methoxy-5-(N-anesulfonyl-N-methylamino)]phenylpiperazine

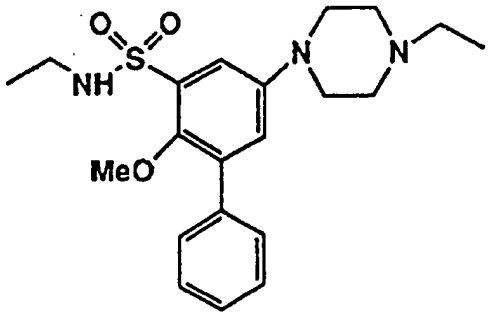
[0203]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(1H, m), 7.5(2H, m), 7.4(3H, m), 6.8(1H, d), 3.7(2H, m), 3.4(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.25(3H, t), 1.15(3H, t).

Example 123 1-Ethyl-4-(3-phenyl-4-methoxy-5-ethylaminosulfonyl)phenylpiperazine

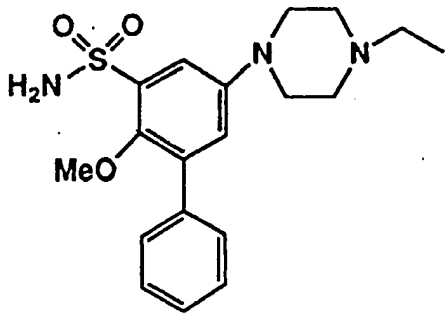
[0204]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, d), 7.4(4H, m), 7.0(1H, d), 5.0(1H, t), 3.4(3H, s), 3.25(4H, m), 3.05(2H, q), 2.6(4H, m), 2.5(2H, q), 1.15(3H, t).

Example 124 1-Ethyl-4-(3-phenyl-4-methoxy-5-aminosulfonyl)phenylpiperazine

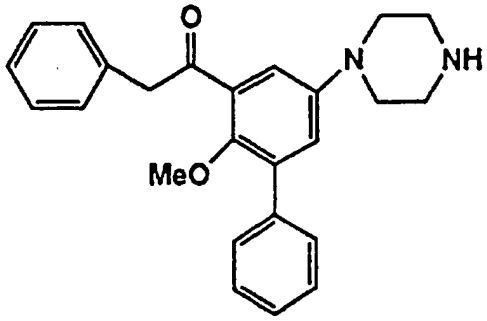
[0205]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, d), 7.4(4H, m), 7.0(1H, d), 5.4(2H, s), 3.4(3H, s), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.1(3H, s).

Example 125 1-(3-Phenyl-4-methoxy-5-phenylacetyl)-phenylpiperazine

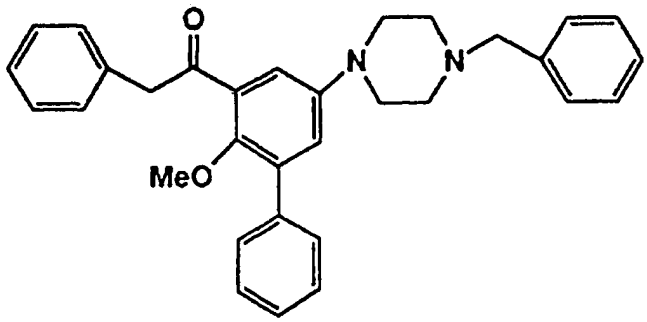
[0206]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.5-7.2(8H, m), 7.0(2H, s), 4.4(2H, s), 3.35(3H, s), 3.1(4H, m), 3.0(4H, m).

Example 126 1-Benzyl-4-(3-phenyl-4-methoxy-5-phenylacetyl)phenylpiperazine

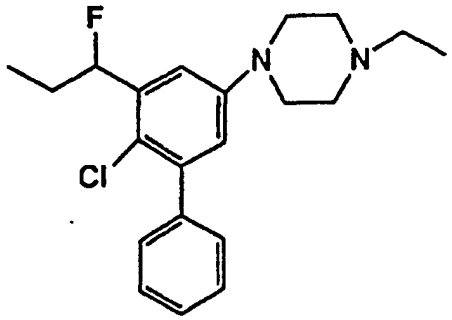
[0207]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.45-7.2(8H, m), 7.0(2H, s), 4.35(2H, s), 3.6(2H, s), 3.35(3H, s), 3.2(4H, m), 2.6(4H, m).

Example 127 1-Ethyl-4-[3-phenyl-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

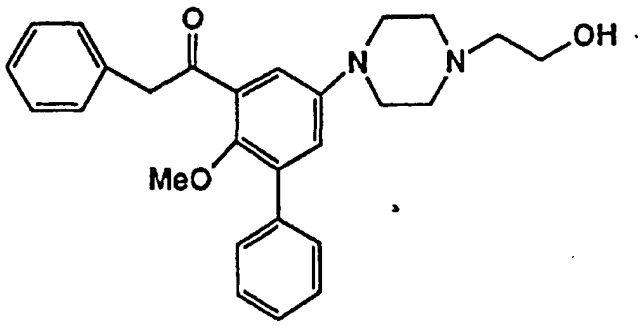
[0208]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4(5H, m), 7.05(1H, d), 6.8(1H, d), 5.8(1H, m), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 2.0(2H, m), 1.15(3H, t), 1.05(3H, t).

Example 128 1-(2-Hydroxyethyl)-4-(3-phenyl-4-methoxy-5-phenylacetyl)phenylpiperazine

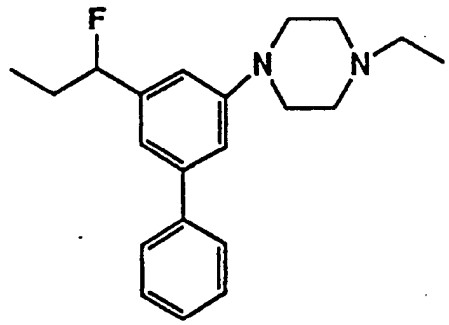
[0209]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.5-7.2(8H, m), 7.0(2H, s), 4.4(2H, s), 3.65(2H, t), 3.35(3H, s), 3.2(4H, m), 2.65(4H, m), 2.6(2H, t).

Example 129 1-Ethyl -4-[3-phenyl-5-(1-fluoropropyl)]-phenylpiperazine

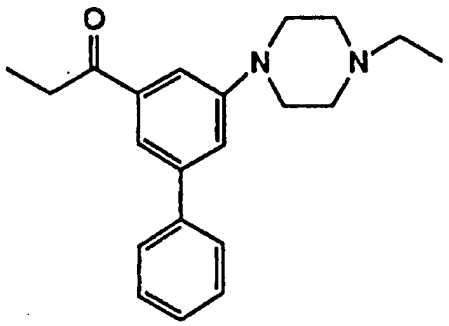
[0210]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(2H, m), 7.35(1H, m), 7.05(1H, s), 6.9(1H, s), 5.4(1H, m), 3.3(4H, m), 2.6(4H, m), 2.5(2H, q), 2.0(2H, m), 1.15(3H, t), 1.0(3H, t).

Example 130 1-Ethyl-4-(3-phenyl-5-propionyl)phenylpiperazine

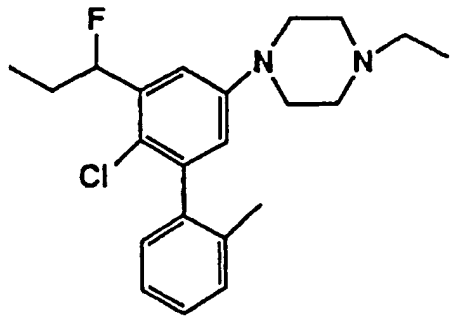
[0211]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.6-7.3(7H, m), 3.35(4H, m), 3.0(2H, q), 2.6(4H, m), 2.5(2H, q), 1.2(3H, t), 1.1(3H, t).

Example 131 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

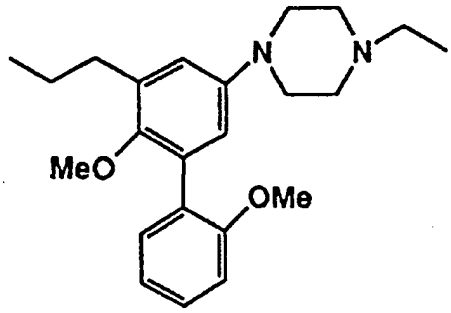
[0212]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 12.9(1H, b-s), 7.4-7.2(3H, m), 7.1(2H, m), 6.8(1H, s), 5.8(1H, m), 3.8-3.6(6H, m), 3.2(2H, b-s), 3.0(2H, b-s), 2.1(3H, d), 1.9(2H, m), 1.5(3H, t), 1.05(3H, t).

Example 132 1-Ethyl-4-[3-(2-methoxyphenyl)-4-methoxy-5-propyl]phenylpiperazine

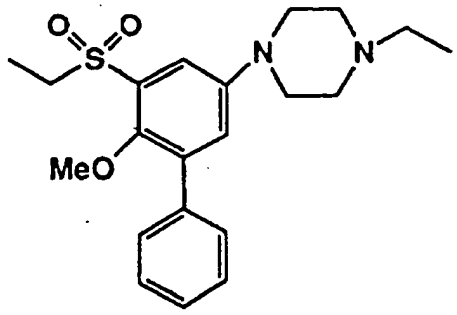
[0213]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3(2H, m), 7.0(2H, m), 6.75(2H, m), 3.8(3H, s), 3.3(3H, s), 3.2(4H, m), 2.6(6H, m), 2.45(2H, q), 1.7(2H, m), 1.15(3H, t), 1.0(3H, t).

Example 133 1-Ethyl-4-(3-phenyl-4-methoxy-5-ethanesulfonyl)phenylpiperazine

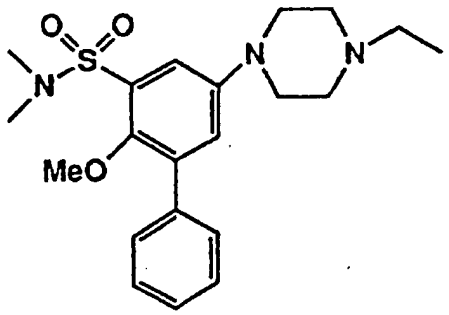
[0214]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.4(4H, m), 7.1(1H, d), 3.5(2H, q), 3.4(3H, s), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 1.3(3H, t), 1.1(3H, t).

Example 134 1-Ethyl-4-(3-phenyl-4-methoxy-5-dimethylaminosulfonyl)phenylpiperazine

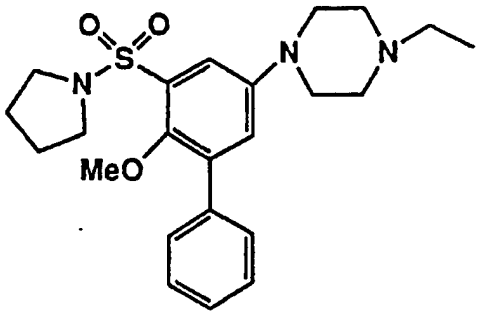
[0215]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, d), 7.5-7.3(4H, m), 7.0(1H, d), 3.4(3H, s), 3.2(4H, m), 2.95(6H, s), 2.6(4H, m), 2.5(2H, q), 1.15(3H, t).

Example 135 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-pyrrolidinylsulfonyl)]phenylpiperazine

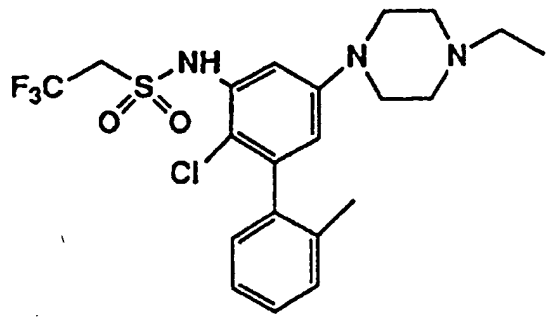
[0216]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.4(4H, m), 7.0(1H, d), 3.45(4H, m), 3.4(3H, s), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 1.9(4H, m), 1.15(3H, t).

Example 136 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(2,2,2-trifluoroethyl)sulfonylamino]phenylpiperazine

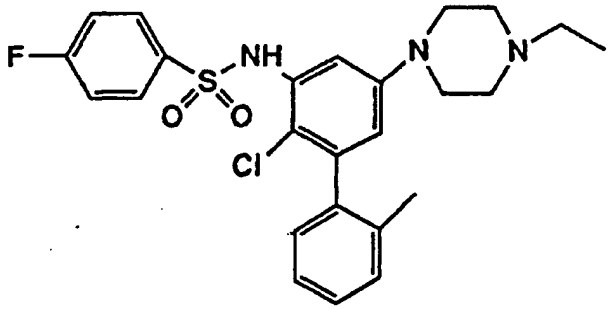
[0217]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4-7.2(4H, m), 7.1(1H, m), 6.6(1H, m), 5.1(1H, b-s), 3.85(2H, q), 3.2(4H, m), 2.65 (4H, m), 2.6(2H, q), 2.1(3H, s), 1.2(3H, t).

Example 137 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(4-fluorophenylsulfonylamino)]phenylpiperazine

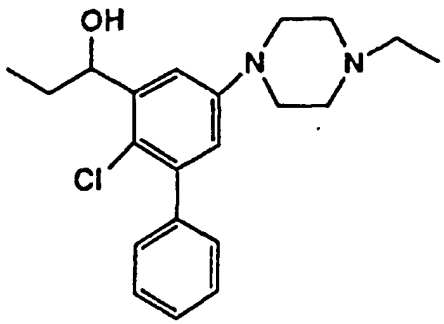
[0218]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.8(2H, m), 7.3-7.1(4H, m), 7.1(2H, m), 7.0(1H, d), 6.55(1H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.85(3H, s), 1.1(3H, t).

Example 138 1-Ethyl-4-[3-phenyl-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine

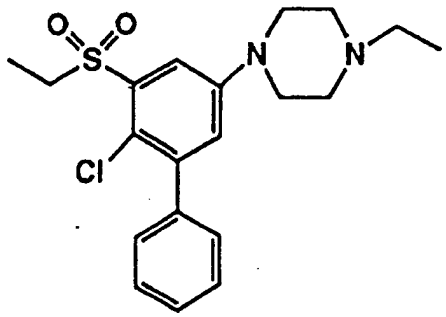
[0219]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.27-7.43(5H, m), 7.16(1H, d), 6.62(1H, d), 5.06(1H, d-d), 3.12(2H, m), 2.95(2H, m), 2.56(4H, m), 2.38-2.54(2H, m), 1.64-1.83(2H, m), 1.17(3H, t), 1.02(3H, t).

Example 139 1-Ethyl-4-(3-phenyl-4-chloro-5-ethanesulfonyl)phenylpiperazine

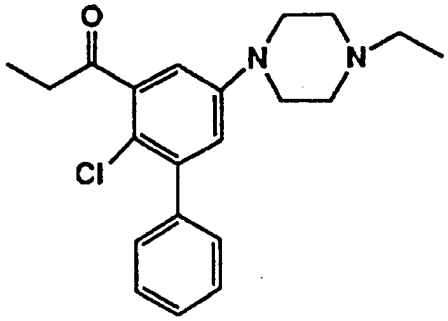
[0220]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7(1H, d), 7.5-7.4(5H, m), 7.0(1H, m), 3.5(2H, q), 3.3(4H, m), 2.6(4H, m), 2.5(2H, q), 1.35(3H, t), 1.15(3H, t).

Example 140 1-Ethyl-4-[3-phenyl-4-chloro-5-propionyl)phenylpiperazine

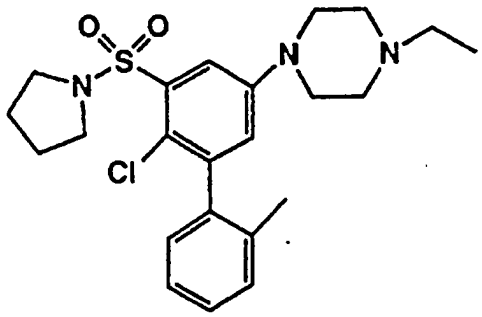
[0221]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.30-7.43(5H, m), 6.89(1H, d), 6.80(1H, d), 3.22(4H, m), 2.94(2H, q), 2.58(4H, m), 2.45(2H, q), 1.22(3H, t), 1.11(3H, t).

Example 141 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-pyrrolidylsulfonyl)]phenylpiperazine

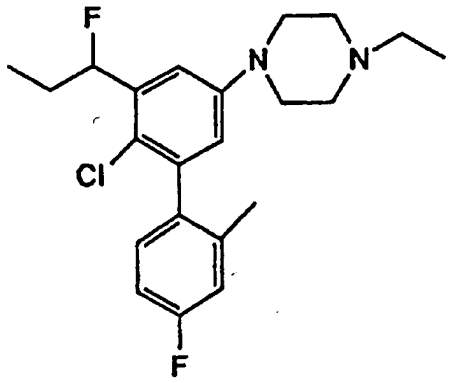
[0222]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7(1H, d), 7.4-7.2(3H, m), 7.1(1H, d), 6.8(1H, m), 3.4(4H, m), 3.3(4H, m), 2.45(2H, q), 2.1(3H, s), 1.9(4H, m), 1.1(3H, t).

Example 142 1-Ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-(1-fluoropropyl)}phenylpiperazine

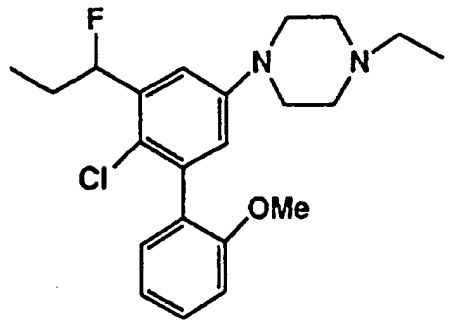
[0223]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1-7.0(2H, m), 7.0-6.9(2H, m), 6.7(1H, d), 5.8(2H, m), 3.2(4H, m), 2.6(4H, m), 2.45 (2H, q), 1.9(2H, m), 2.1(3H, d), 1.1(3H, t), 1.05(3H, m).

Example 143 1-Ethyl-4-[3-(2-methoxyphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

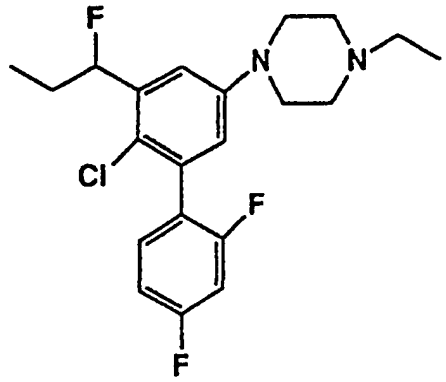
[0224]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4(1H, m), 7.2(1H, m), 7.0(3H, m), 6.8(1H, d), 5.8(1H, m), 3.8(3H, s), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 1.15(3H, t), 1.05(3H, t).

Example 144 1-Ethyl-4-[3-(2.4-difluorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

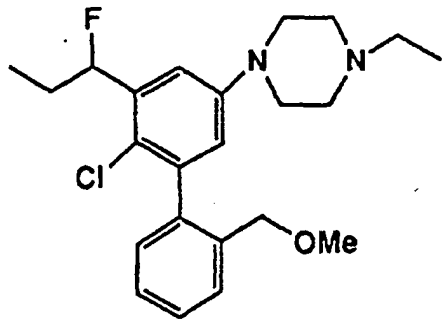
[0225]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.2(1H, m), 7.1(1H, m), 7.0-6.9(2H, m), 6.8(1H, m), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.9(2H, m), 1.1(3H, t), 1.05(3H, m).

Example 145 1-Ethyl-4-[3-(2-methoxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

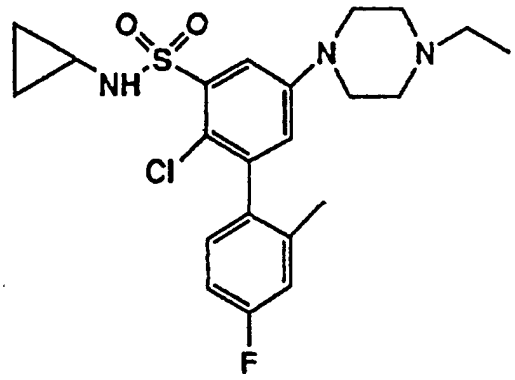
[0226]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(1H, m), 7.1(1H, m), 7.35(1H, m), 7.2(1H, m), 7.05(1H, m), 6.8(1H, m), 5.75 (1H, m), 4.3-4.1(2H, m), 3.2(4H, m), 3.25(3H, d), 2.7(4H, m), 2.55(2H, m), 2.0(2H, m), 1.2(3H, t), 1.05(3H, t).

Example 146 1-Ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-cyclopropaneaminosulfonyl}phenylpiperazine

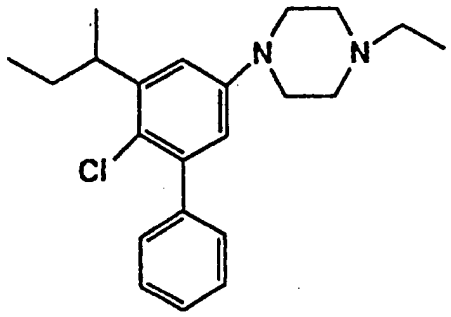
[0227]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.75(1H, s), 7.1-6.8(5H, m), 5.55(1H, s), 3.3(4H, m), 2.6(4H, m), 2.5(2H, q), 2.2 (1H, m), 2.1(3H, s), 1.1(3H, t), 0.7-0.6(4H, m).

Example 147 1-Ethyl-4-[3-phenyl-4-chloro-5-(1-methylpropyl)]phenylpiperazine

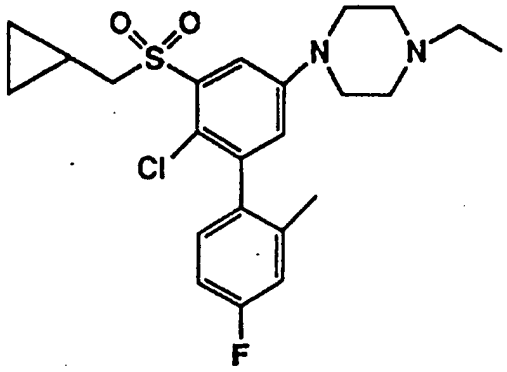
[0228]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4(5H, m), 6.69(2H, d), 6.65(2H, d), 3.18-3.30(1H, m), 3.18(4H, m), 2.60(4H, m), 2.48(2H, m), 1.17-1.92(2H, m), 1.2(3H, d), 1.12(3H, t), 0.89(3H, t).

Example 148 1-Ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-cyclopropylmethylsulfonyl}phenylpiperazine

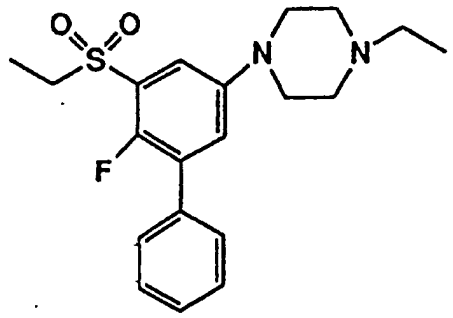
[0229]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.75(1H, d), 7.05(1H, m), 7.0-6.9(3H, m), 3.4(2H, d), 3.3(4H, m), 2.6(4H, m), 2.5 (2H, q), 2.1(3H, s), 1.1(3H, t), 1.0(1H, m), 0.6(2H, m), 0.25(2H, m).

Example 149 1-Ethyl-4-(3-phenyl-4-fluoro-5-ethanesulfonyl)phenylpiperazine

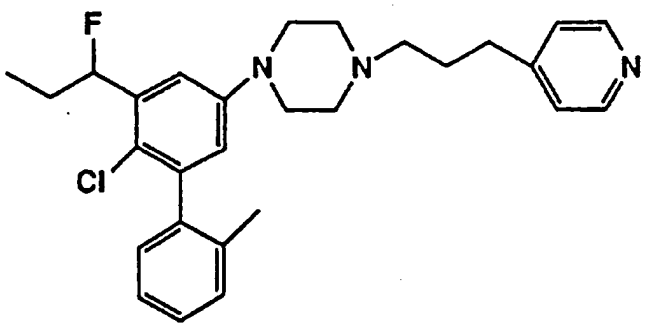
[0230]



NMR($CDCl_3$) d; 7.55-7.4(5H, m), 7.2(1H, m), 3.35(2H, q), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 1.3(3H, t), 1.1(3H, t).

Example 150 1-[3[(4-pyridyl)propyl]-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

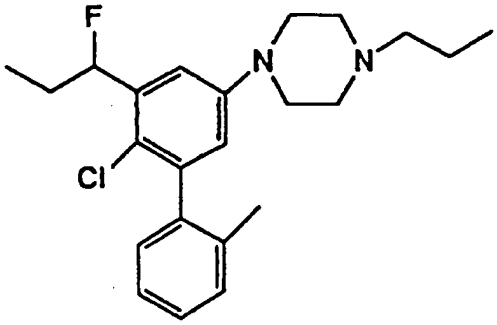
[0231]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.48(2H, d), 7.20-7.32(4H, m), 7.1(2H, d), 7.02(1H, d), 6.71(1H, d), 5.78(1H, d-t), 3.22(4H, m), 2.68(2H, t), 2.60(4H, m), 2.41(2H, t), 2.12(2H, q), 2.08(3H, d), 1.80-1.94(2H, m), 1.07(3H, d-t).

Example 151 1-Propyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

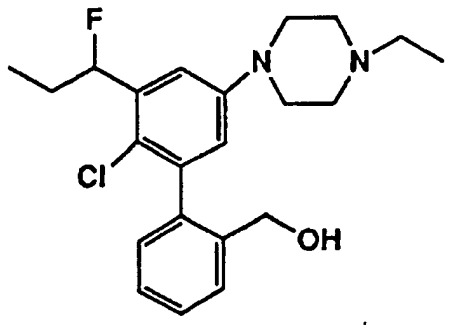
[0232]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1-7.28(4H, m), 7.02(1H, d), 6.70(1H, d), 5.78(1H, d-t), 3.22(4H, m), 2.59(4H, m), 2.37(2H, d-d), 2.11(3H, d), 1.8-1.96(2H, m), 1.5-1.6(2H, m), 1.06(3H, d-t), 0.92(3H, t).

Example 152 1-Ethyl-4-[3-(2-hydroxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

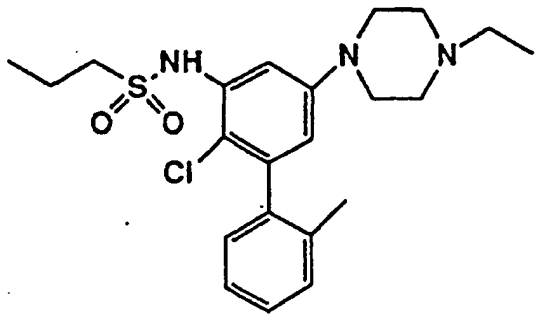
[0233]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(1H, m), 7.45(1H, m), 7.35(1H, m), 7.2(1H, d), 7.05(1H, d), 6.75(1H, d), 5.75 (1H, m), 4.5-4.4(2H, m), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 1.9(2H, m), 1.15(3H, t), 1.05(3H, t).

Example 153 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine

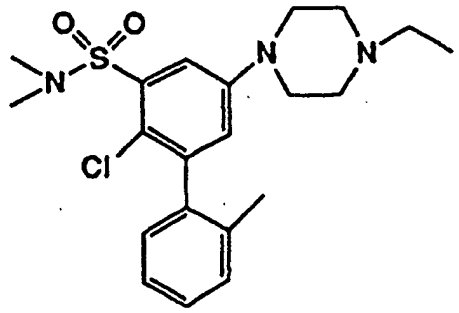
[0234]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4(1H, t), 7.4-7.2(3H, m), 7.2-7.0(2H, m), 3.2(4H, m), 3.1(2H, d-d), 2.6(4H, m), 2.5 (3H, s), 2.45(2H, q), 1.8(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 154 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-dimethylaminosulfonyl]phenylpiperazine

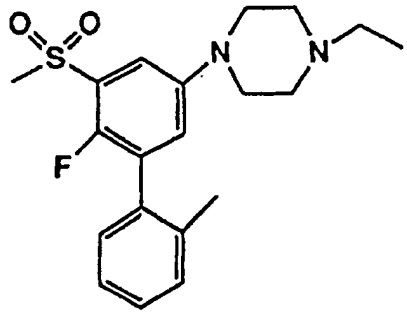
[0235]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.65(1H, t), 7.3-7.2(3H, m), 7.1(1H, m), 6.9(1H, d), 3.25(4H, m), 2.9(6H, s), 2.6(4H, m), 2.45(2H, q), 2.1(3H, s), 1.1(3H, t).

Example 155 1-Ethyl-4-[3-(2-tolyl)-4-fluoro-5-methanesulfonyl]phenylpiperazine

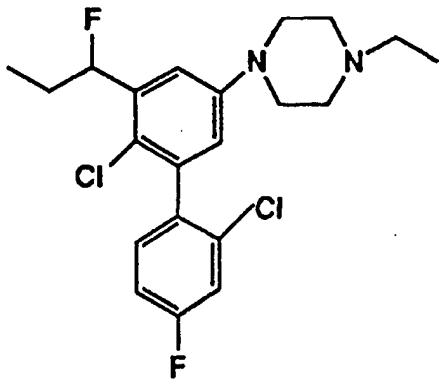
[0236]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4(1H, m), 7.4-7.2(4H, m), 7.0(1H, m), 3.25(4H, m), 3.2(3H, s), 2.6(4H, m), 2.5 (2H, q), 2.2(3H, s), 1.1(3H, t).

Example 156 1-Ethyl-4-[3-(2-chloro-4-fluorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

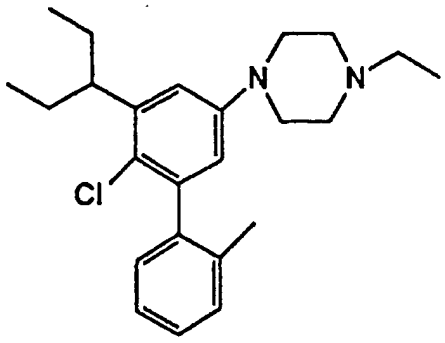
[0237]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4(2H, m), 7.0(2H, m), 6.7(1H, m), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 2.0(2H, m), 1.1(3H, t), 1.05(3H, m).

Example 157 1-Ethyl-4-[3-(2-tolyl-4-chloro-5-(1-ethylpropyl)]phenylpiperazine

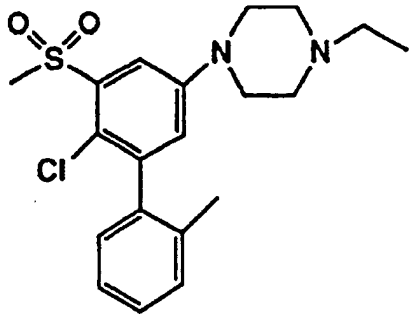
[0238]



^{1}H-NMR(400MHz, $CDCl_3$); 6(ppm) 7.06-7.24(4H, m), 6.74(1H, d), 6.61(1H, d), 3.20(4H, m), 3.15(1H, m), 2.60(4H, m), 2.46(2H, q), 2.00(3H, s), 1.23(3H, t), 1.56-1.74(4H, m), 0.78(3H, t), 0.76(3H, t).

Example 158 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-methanesulfonyl]phenylpiperazine

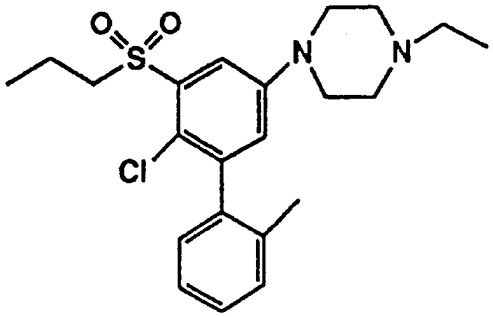
[0239]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7(1H, d), 7.3(3H, m), 7.1(1H, m), 6.95(1H, d), 3.3(3H, s), 3.3(4H, m), 2.6(4H, m), 2.45(2H, q), 2.1(3H, s), 1.1(3H, t).

Example 159 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonyl]phenylpiperazine

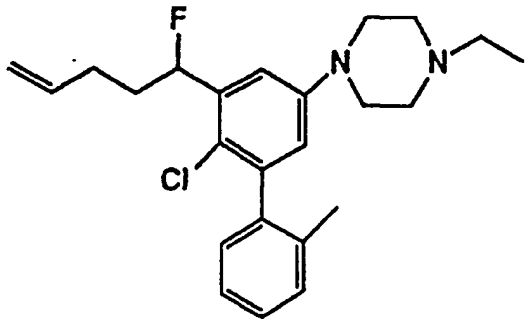
[0240]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.75(1H, m), 7.4-7.2(3H, m), 7.1(1H, d), 6.95(1H, d), 3.4(2H, m), 3.3(4H, m), 2.6 (4H, m), 2.45(2H, q), 2.1(3H, s), 1.8(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 160 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoro-4-pentenyl)]phenylpiperazine

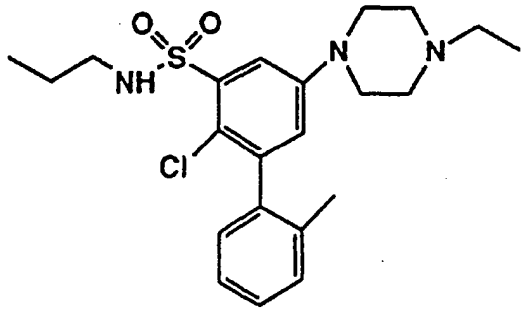
[0241]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.2(4H, m), 7.15(1H, m), 7.05(1H, m), 5.9-5.8(1H, m), 5.1-5.0(2H, m), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 2.3(2H, m), 2.1(3H, m), 2.0(2H, m), 1.1(3H, t).

Example 161 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-propylaminosulfonyl]phenylpiperazine

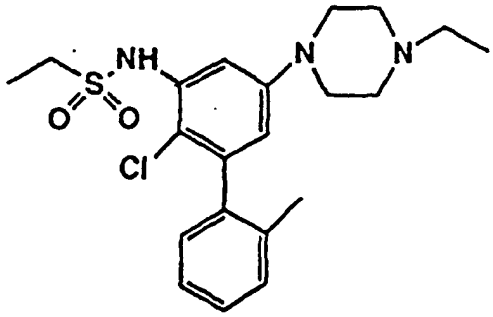
[0242]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.75(1H, d), 7.4-7.2(3H, m), 7.1(1H, d), 6.9(1H, d), 5.1(1H, t), 3.3(4H, m), 2.95(2H, q), 2.6(4H, m), 2.45(2H, q), 2.1(3H, s), 1.5(2H, m), 1.1(3H, t), 0.9(3H, t).

Example 162 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine

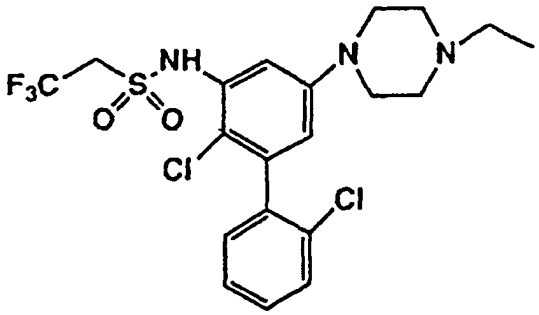
[0243]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7(1H, m), 7.45(1H, m), 7.25(3H, m), 7.1(1H, m), 3.2(4H, m), 3.15(2H, q), 2.6(4H, m), 2.45(2H, q), 2.1(3H, s), 1.4(3H, t), 1.1(3H, t).

Example 163 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(2,2,2-trifluoroethyl)sulfonylamino]phenylpiperazine

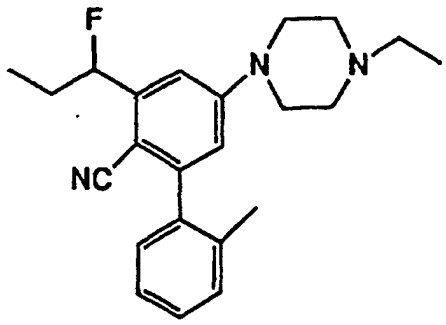
[0244]



^{1}H-NNR(400MHz, $CDCl_3$); δ(ppm) 7.7(2H, m), 7.5(2H, m), 7.4(2H, m), 6.65(1H, d), 3.9(2H, q), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t)

Example 164 1-Ethyl-4- [3-(2-tolyl)-4-cyano-5-(1-fluoropropyl)]phenylpiperazine

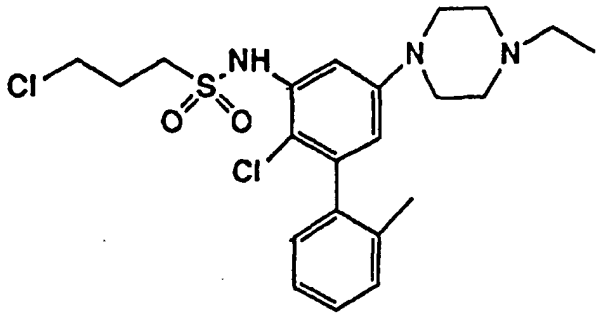
[0245]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.2(4H, m), 7.0(1H, m), 6.65(1H, d), 5.75(1H, m), 3.4(4H, m), 2.6(4H, m), 2.45 (2H, q), 2.2(3H, d), 2.0(2H, m), 1.1(3H, t), 1.05(3H, t).

Example 165 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(3-chloropropyl)sulfonylamino]phenylpiperazine

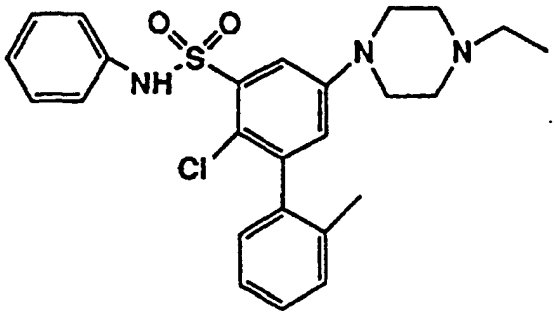
[0246]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7(2H, m), 7.55(1H, m), 7.45(2H, m), 7.3(1H, m), 3.6(2H, t), 3.2(4H, m), 2.6(4H, m), 2.45(2H, m), 2.3(2H, m), 2.1(3H, s), 1.1(3H, t).

Example 166 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-phenylaminosulfonyl]phenylpiperazine

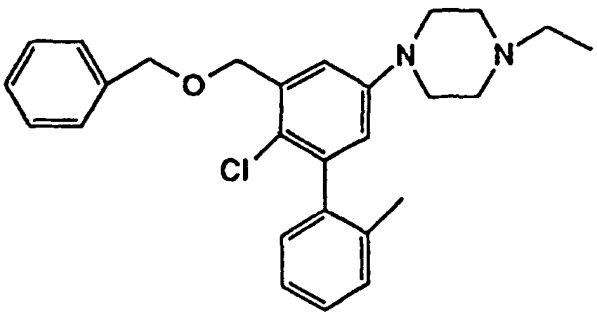
[0247]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(1H, d), 7.4-7.0(9H, m), 6.8(1H, d), 3.2(4H, m), 2.55(4H, m), 2.4(2H, q), 2.0 (3H, s), 1.1(3H, t).

Example 167 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-benzyloxymethyl]phenylpiperazine

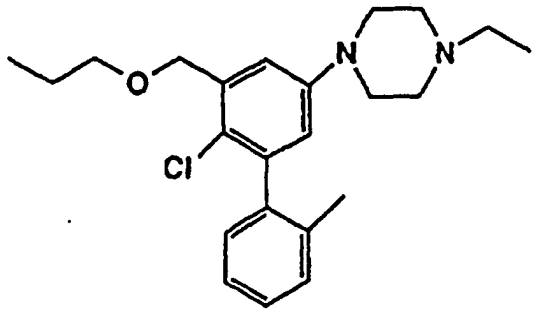
[0248]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.65(1H, m), 7.6-7.1(9H, m), 6.7(1H, d), 4.65(2H, s), 3.2(4H, m), 2.6(4H, m), 2.45 (2H, q), 2.1(3H, s), 1.1(3H, t).

Example 168 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-propoxymethyl]phenylpiperazine

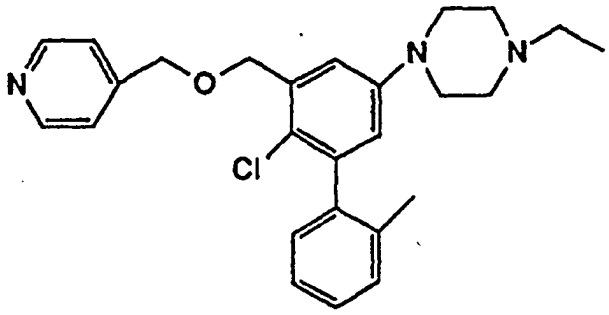
[0249]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.65(1H, m), 7.45(1H, m), 7.3-7.2(2H, m), 7.1(1H, m), 6.7(1H, d), 4.8(2H, s), 3.6 (2H, t), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 2.1(3H, s), 1.7(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 169 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(4-pyridyl)methoxymethyl]phenylpiperazine

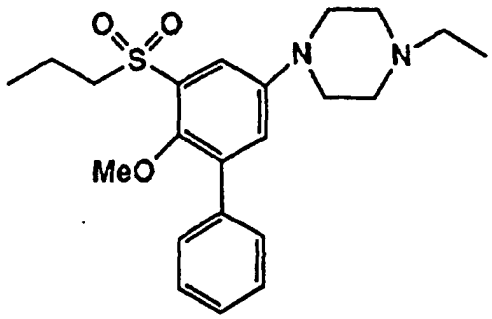
[0250]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.6(2H, m), 7.4-7.2(5H, m), 7.15(2H, m), 6.75(1H, d), 4.71(2H, s), 4.70(2H, s), 3.2 (4H, m), 2.6(4H, m), 2.45(2H, q), 2.1(3H, s), 1.1(3H, t).

Example 170 1-Ethyl-4-(3-phenyl-4-methoxy-5-propanesulfonyl)phenylpiperazine

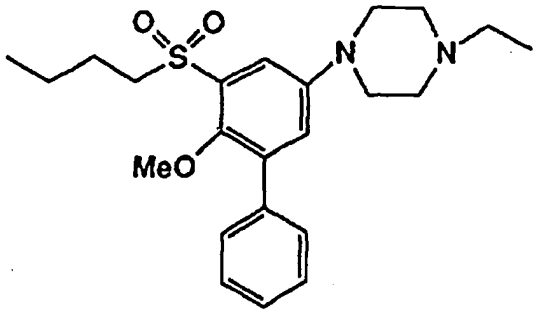
[0251]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(1H, d), 7.4(4H, m), 7.1(1H, m), 3.45(2H, m), 3.4(3H, s), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 1.8(2H, m), 1.15(3H, t), 1.0(3H, t).

Example 171 1-Ethyl-4-(3-phenyl-4-methoxy-5-butanesulfonyl)phenylpiperazine

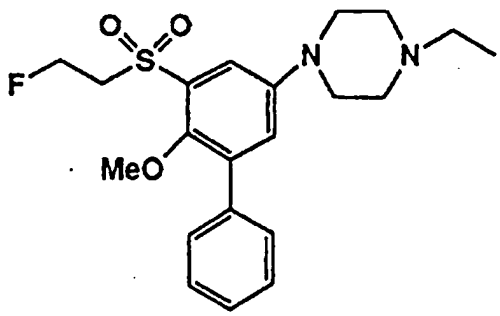
[0252]



^{1}H-NMR(400MHz, $CDCl_3$); 6(ppm) 7.55(1H, d), 7.4(4H, m), 7.1(1H, d), 3.45(2H, m), 3.4(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.75(2H, m), 1.4(2H, m), 1.1(3H, t), 0.95(3H, t).

Example 172 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-fluoroethane)sulfonyl]phenylpiperazine

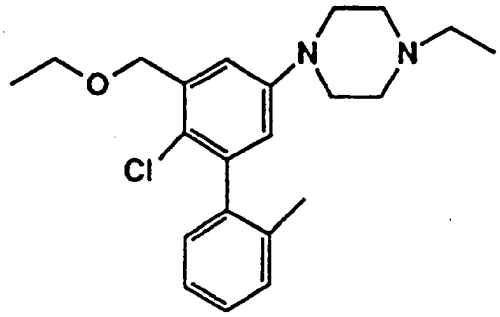
[0253]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(1H, d), 7.4(4H, m), 7.1(1H, m), 4.9(1H, t), 4.8(1H, t), 3.95(1H, t), 3.85(1H, t), 3.4(3H, s), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 1.1(3H, t).

Example 173 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-ethoxymethyl]phenylpiperazine

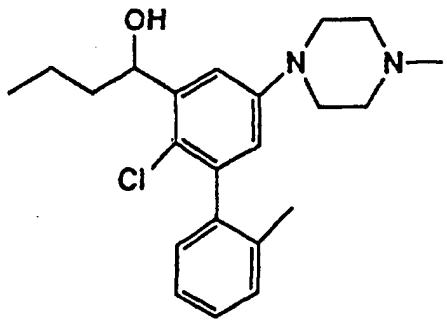
[0254]



^{1}H-NMR(400MHz, $CDCl_3$): δ(ppm) 7.7(1H, m), 7.45(1H, m), 7.25(1H, m), 7.1(2H, m), 6.7(1H, m), 4.6(2H, s), 3.65(2H, q), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 2.1(3H, s), 1.3(3H, t), 1.1(3H, t).

Example 174 1-Methyl-4-[3-(2-tolyl)-4-chloro-5-(1-hydroxybutyl)]phenylpiperazine

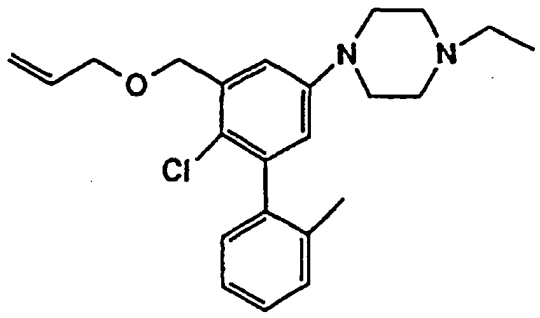
[0255]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.3-7.1(5H, m), 6.65(1H, m), 5.15(1H, m), 3.2(4H, m), 2.6(4H, m), 2.35(3H, s), 2.1 (3H, d), 1.8-1.4(4H, m), 1.0(3H, t).

Example 175 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-allyloxymethyl]phenylpiperazine

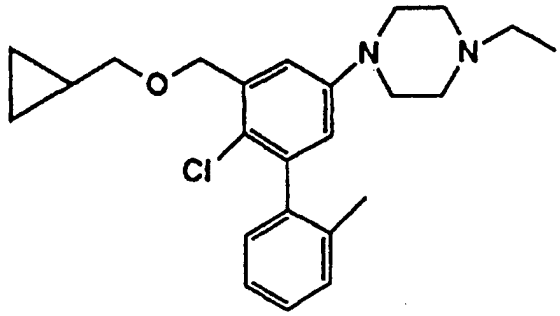
[0256]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.25(3H, m), 7.1(2H, m), 6.7(1H, d), 6.0(1H, m), 5.3(2H, m), 4.6(2H, s), 4.2(2H, m), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 2.1(3H, s), 1.1(3H, t).

Example 176 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-cyclopropylmethoxymethyl]phenylpiperazine

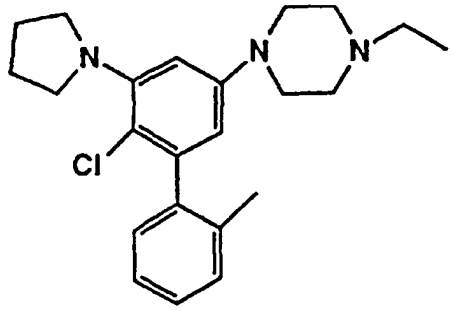
[0257]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.25(3H, m), 7.1(2H, m), 6.7(1H, d), 4.6(2H, s), 3.4(2H, d), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 2.1(3H, s), 1.25(1H, m), 1.1(3H, t), 0.6(2H, m), 0.25(2H, m).

Example 177 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-pyrrolidinyl)]phenylpiperazine

[0258]

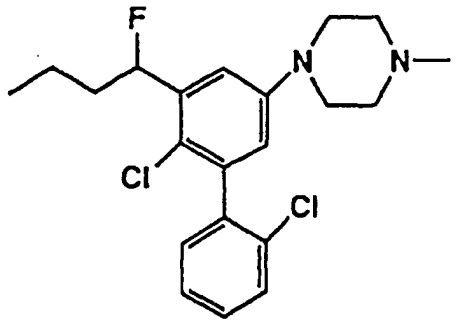


^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.18-7.28(4H, m), 6.21(1H, d), 6.10(1H, d), 3.51(4H, m), 3.26(4H, m), 2.61(1H, d),

2.48(2H, q), 2.30(3H, s), 1.99(4H, m), 1.14(3H, t).

Example 178 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine

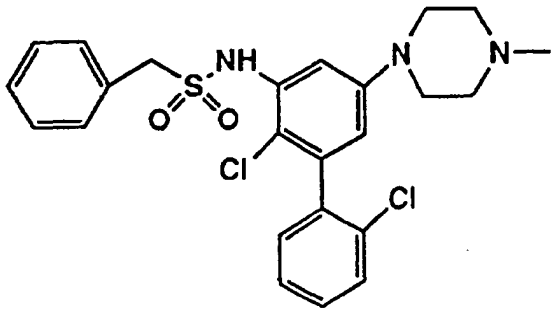
[0259]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.25(3H, m), 7.3(3H, m), 7.1(1H, d), 6.75(1H, d), 5.5(1H, m), 3.2(4H, m), 2.6(4H, m), 2.35(3H, s), 1.9(2H, m), 1.6(2H, m), 1.0(3H, t).

Example 179 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-benzylsulfonylamino]phenylpiperazine

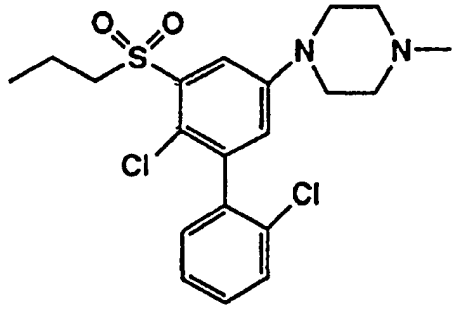
[0260]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(1H, m), 7.4(5H, m), 7.25(4H, m), 6.6(1H, d), 4.4(2H, d-d), 3.2(4H, m), 2.6(4H, m), 2.4(3H, s).

Example 180 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-propanesulfonyl]phenylpiperazine

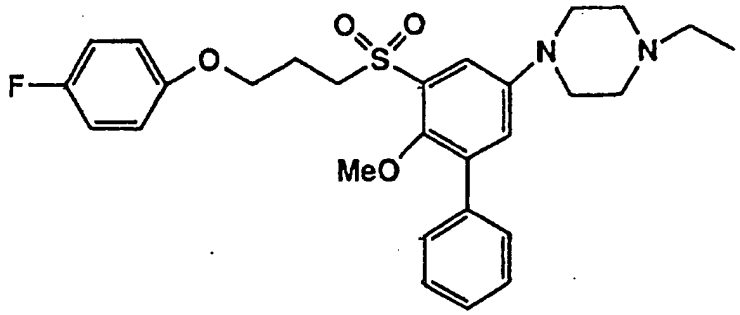
[0261]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7(1H, d), 7.5(1H, m), 7.4(2H, m), 7.25(1H, m), 7.0(1H, d), 3.5-3.4(2H, m), 3.3(4H, m), 2.6(4H, m), 2.4(3H, s). 1.8(2H, m), 1.6(3H, s), 1.0(3H, t).

Example 181 1-Ethyl-4-{3-phenyl-4-methoxy-5-[3-(4-fluorophenoxy)propane]sulfonyl}phenyl]piperazine

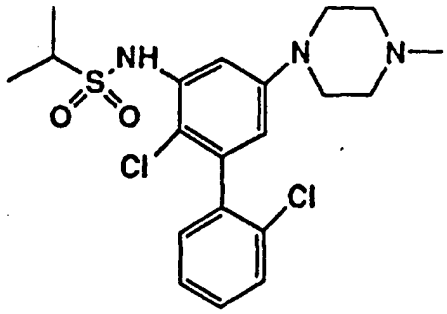
[0262]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.4(3H, m), 7.1(1H, d), 7.0(2H, m), 6.8(2H, m), 4.0(2H, t), 3.7(2H, d-d), 3.4(3H, s), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 2.25(2H, m), 1.1(3H, t).

Example 182 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-isopropylsulfonylamino]phenylpiperazine

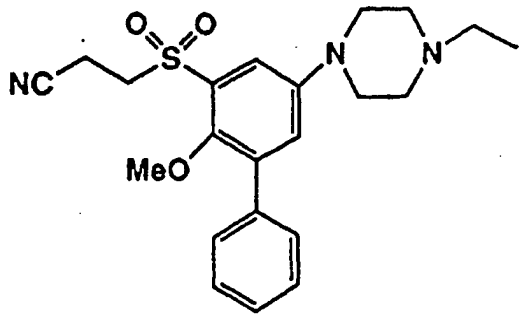
[0263]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.41-7.46(2H, m), 7.30-7.38(2H, m), 7.24(1H, m), 6.60(1H, d), 3.24(1H, m), 3.21 (4H, m), 2.57(4H, m), 2.35(3H, s), 1.96(6H, d).

Example 183 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-cyanoethylsulfonyl)]phenylpiperazine

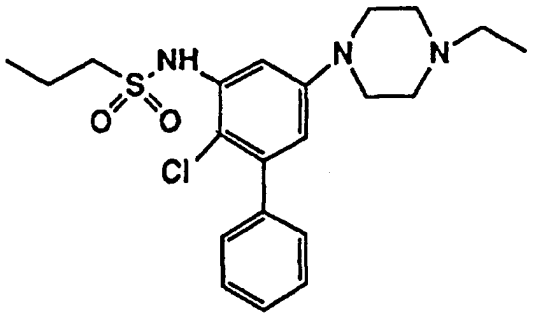
[0264]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.5-7.4(4H, m), 7.15(1H, d), 3.8(2H, t), 3.4(3H, s), 3.25(4H, m), 2.85 (2H, t), 2.6(4H, m), 2.5(2H, q), 1.15(3H, t).

Example 184 1-Ethyl-4-(3-phenyl-4-chloro-5-propanesulfonylamino)phenylpiperazine

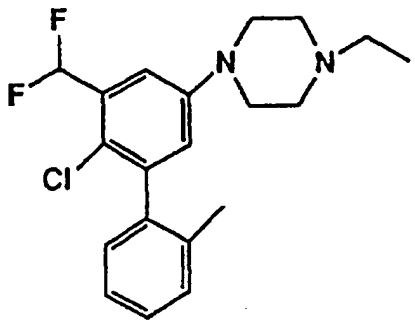
[0265]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.36-7.48(5H, m), 7.24(1H, d), 6.65(1H, d), 3.26(4H, m), 3.10(2H, m), 2.58(4H, m), 2.46(2H, q), 1.82-1.90(2H, m), 1.12(3H, t), 1.02(3H, t).

Example 185 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-difluoromethyl]phenylpiperazine

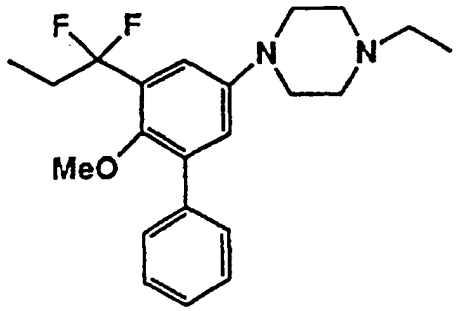
[0266]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4-7.2(4H, m), 7.1(1H, m), 6.85(1H, m), 3.25(4H, m), 2.6(4H, m), 2.45(2H, q), 2.1 (3H, s), 1.1(3H, t).

Example 186 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1,1-difluoropropyl)]phenylpiperazine

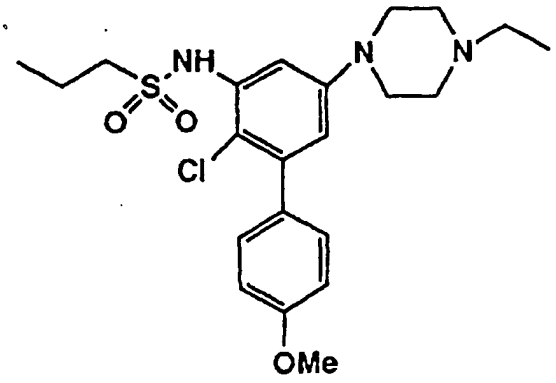
[0267]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(2H, m), 7.4(3H, m), 7.05(1H, d), 6.95(1H, d), 3.25(3H, s), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 2.4(2H, m), 1.15(3H, t), 1.0(3H, t).

Example 187 1-Ethyl-4-[3-(4-methoxyphenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine

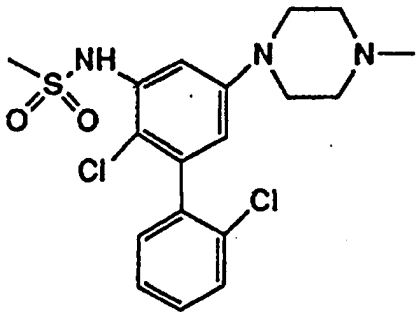
[0268]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.35(2H, m), 7.25(1H, m), 7.0(2H, m), 6.65(1H, m), 3.85(3H, s), 3.25(4H, m), 3.1 (2H, m), 2.6(4H, m), 2.45(2H, q), 1.85(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 188 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-methanesulfonylamino]phenylpiperazine

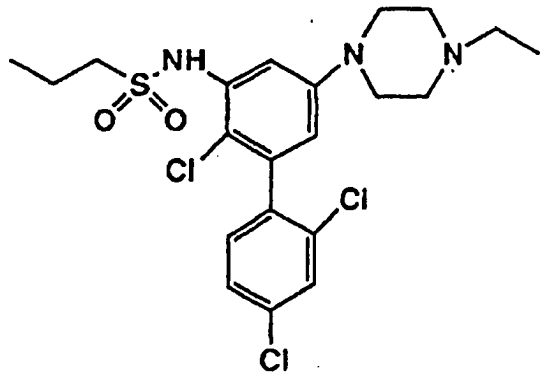
[0269]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.23-7.48(5H, m), 6.62(1H, d), 3.24(4H, m), 3.02(3H, s), 2.54(4H, m), 2.34(3H, s).

Example 189 1-Ethyl-4-[3-(2,4-dichlorophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine

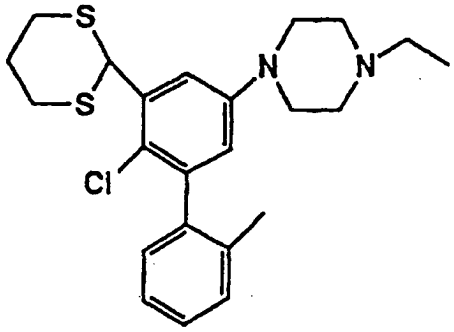
[0270]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7(2H, m), 7.5(2H, m), 7.3(1H, m), 3.25(4H, m), 3.1(2H, m), 2.6(4H, m), 2.45(2H, q), 1.85(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 190 1-Ethyl-4- [3-(2-tolyl)-4-chloro-5-1,3-dithian -2-yl]phenylpiperazine

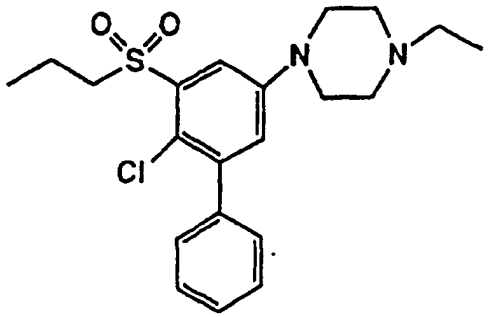
[0271]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.45(2H, d), 7.3-7.2(3H, m), 7.15(1H, d), 6.7(1H, m), 6.1(1H, s), 3.5-3.3(4H, m), 3.2(4H, m), 2.6(4H, m), 2.1(3H, s), 1.1(3H, t).

Example 191 1-Ethyl-4-[3-phenyl-4-chloro-5-propanesulfonyl]phenylpiperazine

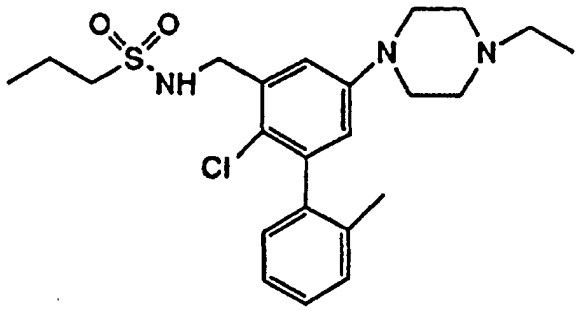
[0272]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.7(2H, m), 7.5-7.4(4H, m), 7.0(1H, d), 3.4(2H, m), 3.3(4H, m), 2.6(4H, m), 2.45 (2H, q), 1.8(2H, m), 1.15(3H, t), 1.0(3H, t).

Example 192 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylaminomethyl]phenylpiperazine

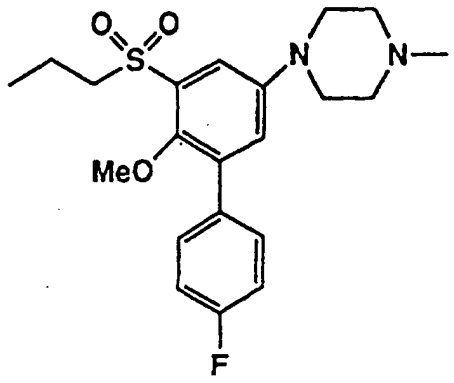
[0273]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.65(2H, m), 7.45(2H, m), 7.1(1H, m), 6.6(1H, d), 3.2(4H, m), 3.1(2H, m), 2.6(4H, m), 2.45(2H, q), 2.1(3H, s), 1.85(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 193 1-Methyl-4-[3-(4-fluorophenyl)-4-methoxy-5-propanesulfonyl]phenylpiperazine

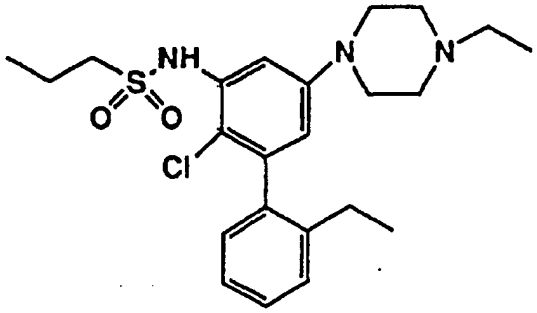
[0274]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.4(1H, d), 7.2(2H, m), 7.05(1H, d), 3.4(2H, m), 3.4(3H, s), 3.25(4H, m), 2.6(4H, m), 2.4(3H, s), 1.8(2H, m), 1.05(3H, t).

Example 194 1-Ethyl-4-[3-(2-ethylphenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine

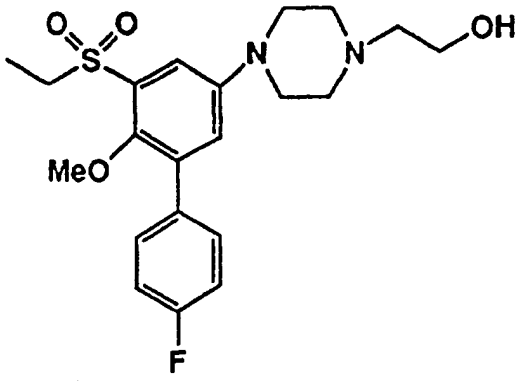
[0275]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4-7.2(4H, m), 7.1(1H, d), 6.6(1H, d), 3.25(4H, m), 3.1(2H, m), 2.6(4H, m), 2.5-2.3(4H, m), 1.85(2H, m), 1.2-1.0(9H, m).

Example 195 1-(2-Hydroxyethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine

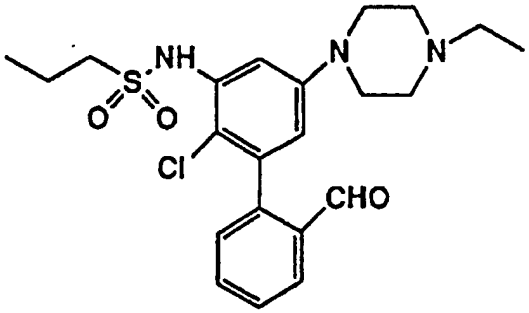
[0276]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.4(1H, d) 7.2(2H, m), 7.05(1H, d), 3.7(2H, t), 3.5(2H, q), 3.4(3H, s), 3.2(4H, m), 2.7(4H, m), 2.6(2H, t), 1.3(3H, t).

Example 196 1-Ethyl-4-[3-(2-formylphenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine

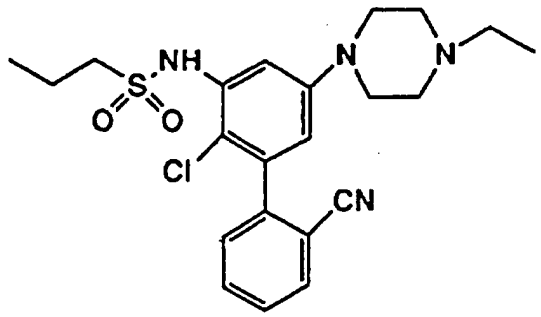
[0277]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 9.8(1H, s), 8.0(1H, d), 7.35(2H, m), 6.6(1H, m), 3.3(4H, m), 3.1(2H, m), 2.6(4H, m), 2.5(2H, q), 1.9(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 197 1-Ethyl-4-[3-(2-cyanophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine

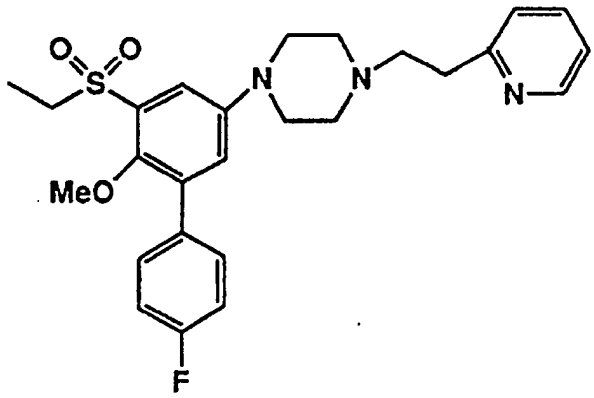
[0278]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.8(1H, d), 7.7(2H, m), 7.5(2H, m), 6.6(1H, m), 3.3(4H, m), 3.1(2H, m), 2.6(4H, m), 2.5(2H, q), 1.9(2H, m), 1.1(3H, t), 1.0(3H, t).

Example 198 1-[2-(2-Pyridyl)ethyl]-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine

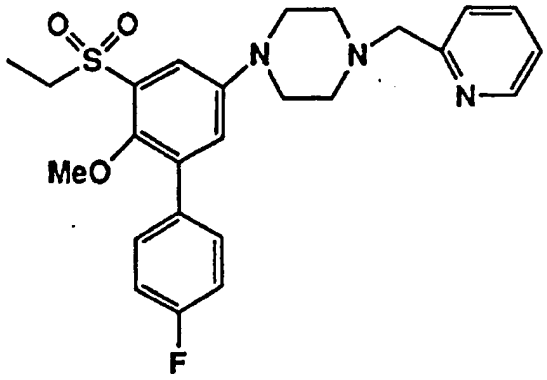
[0279]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.6(1H, m), 7.6(1H, m), 7.55(2H, m), 7.4(1H, d), 7.2(1H, d), 7.15(3H, m), 7.05(1H, d), 3.5(2H, q), 3.4(3H, s), 3.25(4H, m), 3.0(2H, m), 2.8(2H, m), 2.7(4H, m), 1.3(3H, t).

Example 199 1-(2-Pyridylmethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine

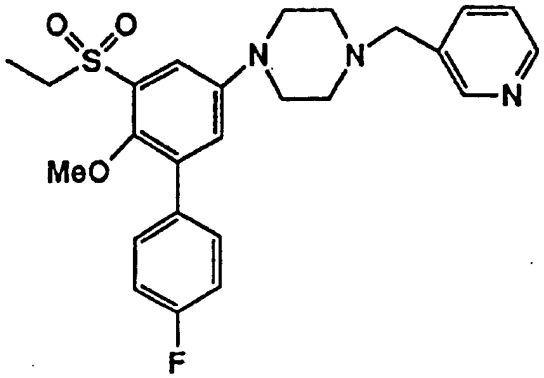
[0280]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.6(1H, m), 7.7(1H, m), 7.55(2H, m), 7.4(2H, m), 7.2-7.1(3H, m), 7.05(1H, d), 3.75 (2H, s), 3.5(2H, q), 3.4(3H, s), 3.3(4H, m), 2.7(4H, m), 1.3(3H, t).

Example 200 1-(3-Pyridylmethyl))-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine

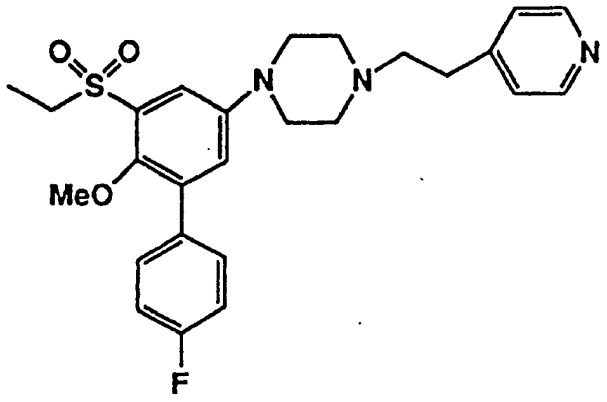
[0281]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.6(1H, s), 8.55(1H, m), 7.7(1H, m), 7.55(2H, m), 7.4(1H, d), 7.3(1H, m), 7.2(2H, m), 7.0(1H, d), 3.6(2H, s), 3.5(2H, q), 3.4(3H, s), 3.2(4H, m), 2.6(4H, m), 1.3(3H, t), 1.2(3H, t).

Example 201 1-[2-(4-Pyridyl)ethyl]-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine

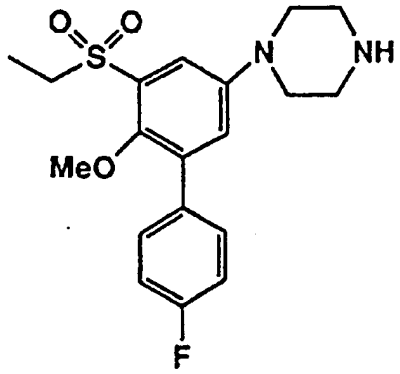
[0282]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.5(2H, m), 7.55(2H, m), 7.45(1H, d), 7.2(4H, m), 7.05(1H, d), 3.5(2H, q), 3.4(3H, s), 3.25(4H, m), 2.8(2H, m), 2.7(6H, m), 1.3(3H, t), 1.2(3H, t).

Example 202 1-[3-(4-Fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine

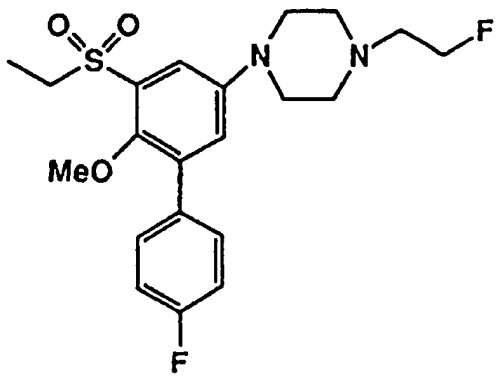
[0283]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.45(1H, s), 7.2(2H, m), 7.05(1H, d), 3.9(1H, b-s), 3.5(2H, q), 3.4(3H, s), 3.25(4H, m), 3.1(4H, m), 1.3(3H, t).

Example 203 1-(2-Fluoroethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine

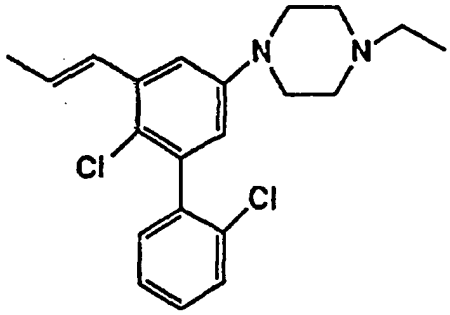
[0284]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.55(2H, m), 7.4(1H, m), 7.15(2H, m), 7.05(1H, d), 4.6(2H, m), 3.5(2H, q), 3.4(3H, s), 3.25(4H, m), 2.75(2H, d-t), 2.7(4H, m), 1.3(3H, m).

Example 204 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-propenyl)]phenylpiperazine

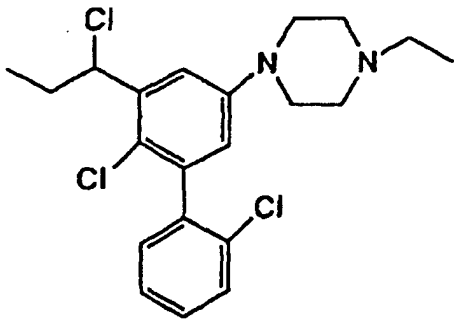
[0285]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(1H, m), 7.3(3H, m), 7.05(1H, m), 6.8(1H, m), 6.7(1H, d), 6.2(1H, m), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 1.95(3H, d), 1.15(3H, t).

Example 205 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-chloropropyl)]phenylpiperazine

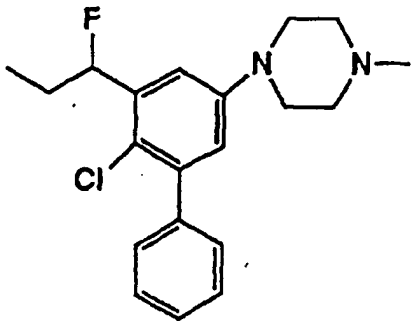
[0286]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.46(1H, m), 7.17-7.36(4H, m), 6.73(1H, d), 5.40(1H, m), 3.23(4H, m), 2.60(4H, m), 2.46(2H, q), 2.02-2.13(2H, m), 1.13(3H, t), 1.08(3H, t).

Example 206 1-Methyl-4-[3-phenyl-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

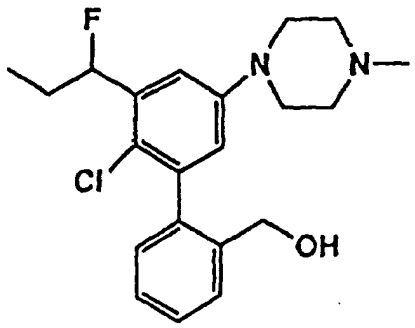
[0287]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4(5H, m), 7.05(1H, d), 6.8(1H, s), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.35(3H, s), 2.0(2H, m), 1.05(3H, t).

Example 207 1-Methyl-4-[3-(2-hydroxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

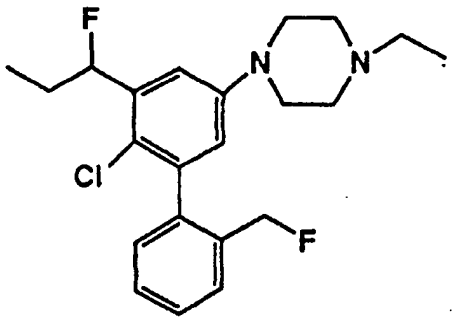
[0288]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.5(1H, m), 7.3(3H, t), 7.35(1H, m), 7.2(1H, d), 7.05(1H, d), 6.75(1H, d), 5.75(1H, m), 4.45(2H, m), 3.2(4H, m), 2.6(4H, m), 2.3(3H, s), 2.0(2H, m), 1.05(3H, t).

Example 208 1-Ethyl-4-[3-(2-fluoromethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

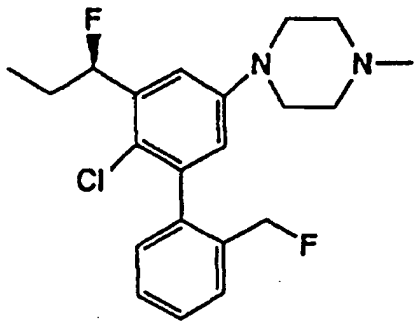
[0289]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(1H, m), 7.4(2H, m), 7.2(1H, d), 7.05(1H, d), 6.8(1H, d), 5.75(1H, m), 5.3-5.0 (2H, m), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 2.0(2H, m), 1.1(3H, t), 1.05(3H, t).

Example 209 1-Methyl-4-{3-(2-fluoromethylphenyl)-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine

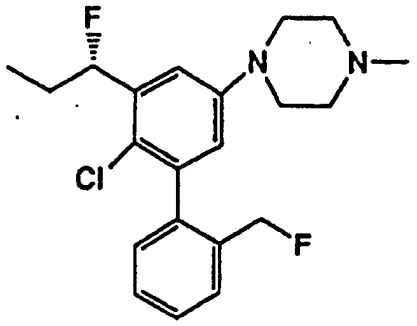
[0290]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(1H, m), 7.4(2H, m), 7.2(1H, d), 7.05(1H, d), 6.8(1H, d), 5.75(1H, m), 5.3-5.0 (2H, m), 3.2(4H, m), 2.6(4H, m), 2.35(3H, s), 1.9(2H, m), 1.05(3H, t).

Example 210 1-Methyl-4-{3-(2-fluoromethylphenyl)-4-chloro-5-[1-(S)-fluoropropyl]}phenylpiperazine

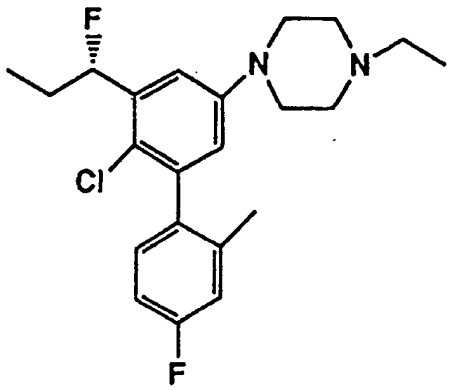
[0291]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.6(1H, m), 7.4(2H, m), 7.2(1H, d), 7.05(1H, d), 6.8(1H, d), 5.75(1H, m), 5.3-5.0 (2H, m), 3.2(4H, m), 2.6(4H, m), 2.35(3H, s), 1.9(2H, m), 1.05(3H, t).

Example 211 1-Ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-[1-(S)-fluoropropyl]}phenylpiperazine

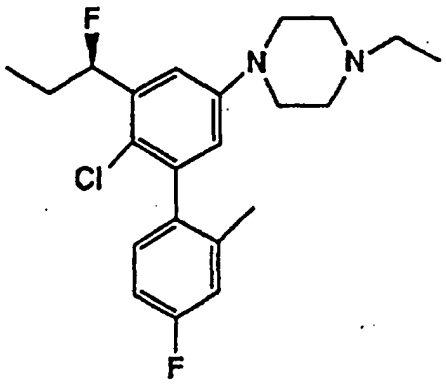
[0292]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1-7.0(2H, m), 7.0-6.9(2H, m), 6.7(1H, d), 5.75(1H, m), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 2.1(3H, d), 1.15(3H, t), 1.05(3H, m).

Example 212 1-Ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine

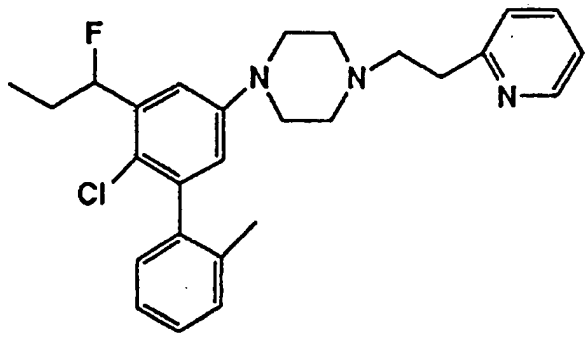
[0293]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1-7.0(2H, m), 7.0-6.9(2H, m), 6.7(1H, d), 5.75(1H, m), 3.25(4H, m), 2.6(4H, m), 2.5(2H, q), 2.1(3H, d), 1.15(3H, t), 1.05(3H, m).

Example 213 1-[2-(2-Pyridyl)ethyl]-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

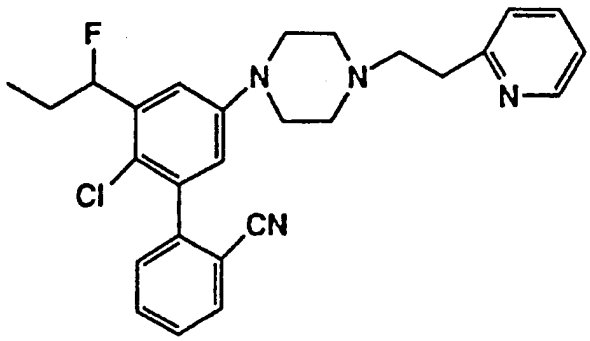
[0294]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.55(1H, d), 7.6(1H, m), 7.3-7.2(4H, m), 7.1(2H, m), 7.05(1H, d), 6.7(1H, d), 5.8 (1H, m), 3.2(4H, m), 3.0(2H, m), 2.8(2H, m), 2.7(4H, m), 2.1(3H, d), 1.9(2H, m), 1.05(3H, m).

Example 214 1-[2-(2-Pyridyl)ethyl]-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

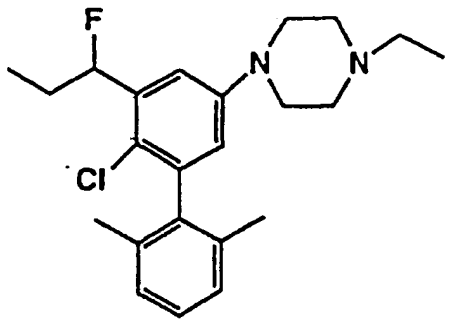
[0295]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.55(1H, d), 7.8(1H, d), 7.6(2H, m), 7.45(2H, m), 7.2(1H, d), 7.1(2H, m), 6.8(1H, d), 5.8(1H, m), 3.25(4H, m), 3.0(2H, m), 2.8(2H, m), 2.7(4H, m), 2.0(2H, m), 1.05(3H, t).

Example 215 1-Ethyl-4-[3-(2,6-xylyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

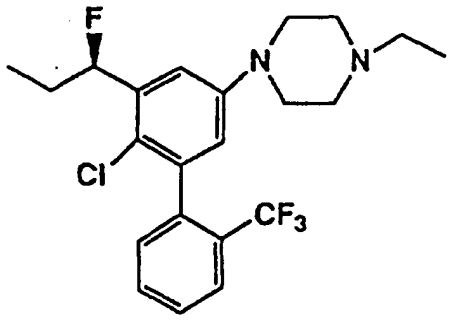
[0296]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.2-7.0(4H, m), 6.65(1H, d), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.5(2H, q), 2.0(6H, d), 1.9(2H, m), 1.15(3H, t), 1.05(3H, t).

Example 216 1-Ethyl-4-{3-(2-trifluoromethylphenyl)-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine

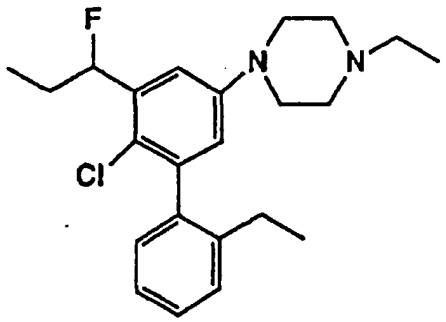
[0297]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.8(1H, m), 7.6(111, m), 7.5(1H, m), 7.25(1H, m), 7.05(1H, d), 6.75(1H, m), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.9(2H, m), 1.15(3H, t), 1.05(3H, d-t).

Example 217 1-Ethyl-4-[3-(2-ethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

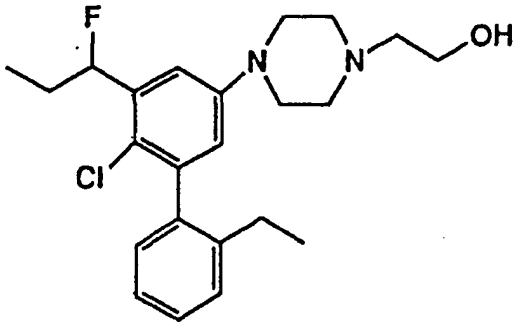
[0298]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4-7.2(3H, m), 7.1(1H, d), 7.05(1H, m), 6.75(1H, d), 5.8(1H, m), 3.2(4H, m), 2.6 (4H, m), 2.5-2.3(4H, m), 1.9(2H, m), 1.2-1.0(6H, m).

Example 218 1-(2-Hydroxyethyl)-4-[3-(2-ethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine

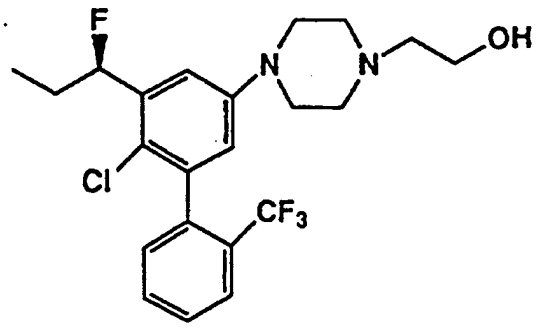
[0299]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.4-7.2(3H, m), 7.1(1H, d), 7.05(1H, d), 6.75(1H, d), 5.8(1H, d), 3.6(2H, t), 3.2(4H, m), 2.65(4H, m), 2.60(2H, t), 2.40(2H, m), 1.9(2H, m), 1.05(6H, m).

Example 219 1-(2-Hydroxyethyl)-4-{3-(2-trifluoromethylphenyl)-4-chloro-5-[1-(R)-fluoropropyl]}phenyl]piperazine

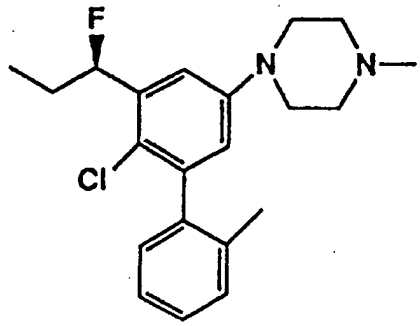
[0300]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.8(1H, m), 7.6(1H, m), 7.5(1H, m), 7.25(1H, m), 7.05(1H, d), 6.75(1H, m), 5.8(1H, m), 3.2(4H, m), 2.6(4H, m), 2.45(2H, q), 1.9(2H, m), 1.15(3H, t), 1.05(3H, d-t).

Example 220 1-Methyl-4-{3-(2-tolyl)-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine

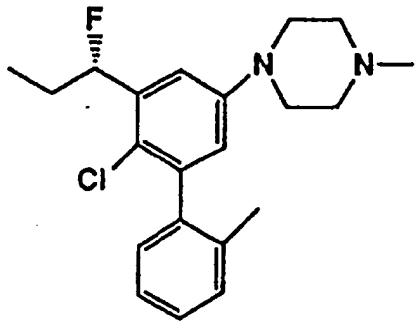
[0301]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.09-7.28(4H, m), 7.03(2H, d), 6.71(2H, d), 5.78(1H, m), 3.22(4H, m), 2.58(4H, m), 2.37(3H, s), 2.12(3H, d), 1.82-2.03(2H, m), 1.07(3H, d-t).

Example 221 1-Methyl-4-{3-(2-tolyl)-4-chloro-5-[1-(S)-fluoropropyl]}phenylpiperazine

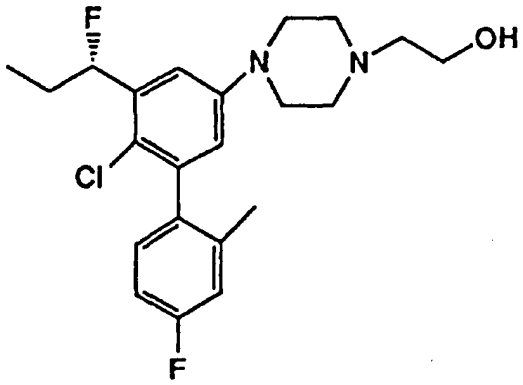
[0302]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.09-7.28(4H, m), 7.03(2H, d), 6.71(2H, d), 5.78(1H, m), 3.22(4H, m), 2.58(4H, m), 2.37(3H, s), 2.12(3H, d), 1.82-2.03(2H, m), 1.07(3H, d-t).

Example 222 1-(2-Hydroxyethyl)-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-[1-(S)-fluoropropyl]}phenylpiperazine

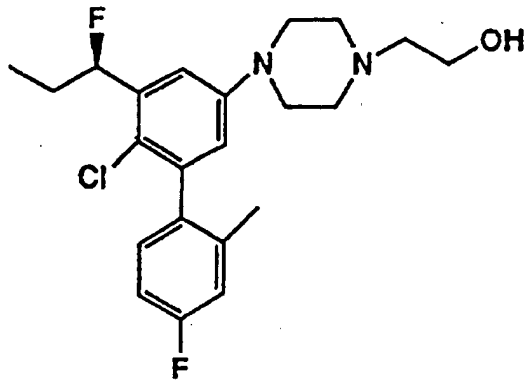
[0303]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.8(1H, m), 6.95(2H, m), 6.7(1H, d), 5.8(1H, m), 3.7(2H, m), 3.2(4H, m), 2.7(4H, m), 2.6(2H, m), 2.1(3H, d), 1.9(2H, m), 1.05(3H, m).

Example 223 1-(2-Hydroxyethyl)-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine

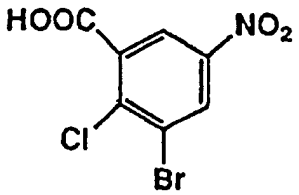
[0304]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 7.1(2H, m), 6.95(2H, m), 6.7(1H, d), 5.8(1H, m), 3.7(2H, m), 3.2(4H, m), 2.7(4H, m), 2.6(2H, m), 2.1(3H, d), 1.9(2H, m), 1.05(3H, m).

Example 224 Synthesis of 2-chloro-3-bromo-5-nitrobenzoic acid

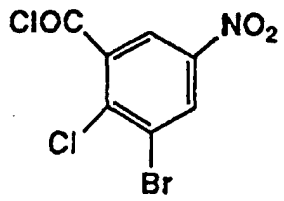
[0305]



[0306] 26.63 g (86.3 mmol) of ethyl 2-chloro-3-bromo-5-nitrobenzoate was dissolved in a mixture comprising 150 ml of ethanol and 80 ml of THF, followed by the addition of 55 ml of a 2N aqueous solution of sodium hydroxide. The obtained mixture was stirred at room temperature for one hour, followed by the addition of water and 19 ml of 6N hydrochloric acid. The obtained mixture was concentrated under reduced pressure and extracted with ethyl acetate. The ethyl acetate phase was washed with a saturated aqueous solution of common salt, dried and distilled to remove the solvent, giving 24.11 g of the title compound (yield: quantitative).
m.p.; 162-163.5°C
^{1}H-NMR(400MHz, DMSO-d_6); δ(ppm) 8.47(1H, d, J=2.7Hz), 8.68(1H, d, J=2.7Hz).
MS m/z: 280[M-H]$^-$, 278[M-H]$^-$.

Example 225 Synthesis of 2-chloro-3-bromo-5-nitrobenzoyl chloride

[0307]



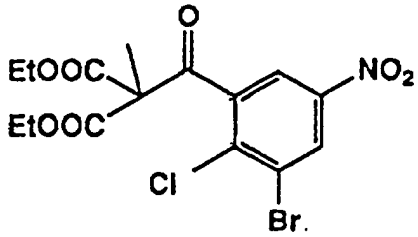
[0308] 5.1 ml (69.9 mmol) of thionyl chloride and a solvent mixture comprising 50 ml of benzene and 0.2 ml. of DMF were added to 14.07 g (50.2 mmol) of 2-chloro-3-bromo-5-nitrobenzoic acid. The obtained mixture was heated under reflux for 2 hours and distilled to remove the solvent. Benzene was added to the residue and the obtained mixture was distilled again to remove the solvent. Thus, 15.07 g of the title compound was obtained (yield: quantitative).

[0309] This product was used in the following reaction without any additional purification.

^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 8.71(1H, d, J=2.7Hz), 8.74(1H, d, J=2.7Hz).

Example 226 Synthesis of diethyl 2-(2-chloro-3-bromo-5-nitrobenzoyl)-2-methylmalonate

[0310]



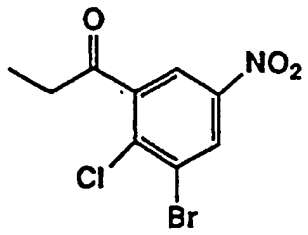
[0311] 2.2 g of 55% sodium hydride was suspended in 30 ml of THF, followed by the addition of 50 ml of a THF solution of 8.65 ml (50.3 mmol) of diethyl methylmalonate under cooling with ice. The obtained mixture was stirred at room temperature for 20 minutes and cooled with ice again, followed by the dropwise addition of 85 ml of a THF solution of the 2-chloro-3-bromo-5-nitrobenzoyl chloride prepared in the above Example. The obtained mixture was stirred as such for 1.5 hours and then poured into an aqueous solution of ammonium chloride. The resulting mixture was extracted with ethyl acetate. The ethyl acetate phase was washed with a saturated aqueous solution of sodium hydrogen carbonate and a saturated brine, dried and distilled to remove the solvent. 30 ml of methylene chloride was added to the residue. The resulting mixture was freed from insolubles by filtration and concentrated under reduced pressure to give 21.77 g of the title compound (yield: quantitative).

m.p.; 75~76.5°C

^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.24(6H, t, J=7.1Hz), 1.84(3H, s), 4.22(2H, q, J=7.1Hz), 4.23(2H, q, J=7.1Hz), 8.43 (1H, d, J=2.6Hz), 8.55(1H, d, J=2.6Hz). MS m/z: 438[MH]$^+$, 436[MH]$^+$.

Example 227 Synthesis of 2-chloro-3-bromo-5-nitropropiophenone

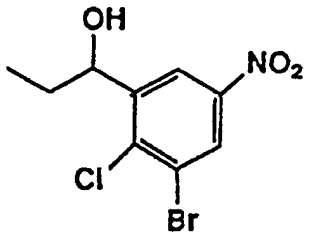
[0312]



[0313] 90 ml of acetic acid, 14.0 ml of concentrated hydrochloric acid and 7.0 ml of concentrated sulfuric acid were added to 21.72 g of diethyl 2-(2-chloro-3-bromo-5-nitrobenzoyl)-2-methylmalonate. The obtained mixture was heated under reflux for 13 hours and then poured into a mixture comprising 350 ml of ice-water and 100 ml of ethyl acetate. The resulting mixture was extracted with ethyl acetate. The ethyl acetate phase was washed with a saturated brine and a saturated aqueous solution of sodium hydrogen carbonate successively, dried and distilled to remove the solvent, giving 10.56 g of the title compound (yield: 72%).
m.p.; 81.5-83°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.25(3H, t, J=7.1Hz), 2.96(2H, q, J=7.1Hz), 8.17(1H, d, J=2.6Hz), 8.57(1H, d, J=2.6Hz).
MS m/z: 292[MH]$^+$, 294[MH]$^+$, 296[MH]$^+$.

Example 228 Synthesis of 1-(2-chloro-3-bromo-5-nitrophenyl)-1-propanol

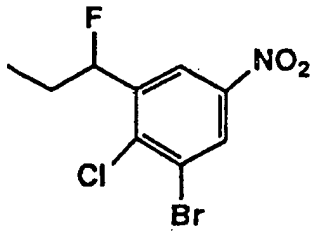
[0314]



[0315] 7.48 g (25.6 mmol) of 2-chloro-3-bromo-5-nitropropiophenone was dissolved in 50 ml of methanol, followed by the addition of 735 mg (19.4 mmol) of sodium borohydride under cooling with ice. The obtained mixture was stirred for 30 minutes, followed by the addition of an aqueous solution of ammonium chloride. The resulting mixture was extracted with ethyl acetate. The ethyl acetate phase was washed with a saturated brine, dried and distilled to remove the solvent, giving 7.42 g of the title compound (yield: quantitative).
m.p.; 110-113°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.05(3H, t, J=7.5Hz), 1.69(1H, m), 1.88(1H, m), 2.15(1H, d, J=4.0Hz), 5.13(1H, dt, J=7.9, 4.0Hz), 8.42(1H, d, J=2.6Hz), 8.46(1H, d, J=2.6Hz).
MS m/z: 295[M-H]$^-$, 293[M-H]$^-$.

Example 229 Synthesis of 3-bromo-4-chloro-5-(1fluoropropyl)-1-nitrobenzene

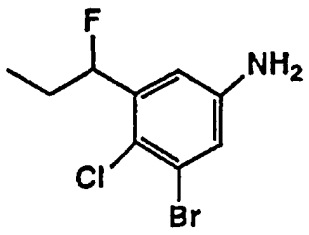
[0316]



[0317] 9.0 ml of hexafluoropropenediethylamine and 80 ml of a chloroform solution of 7.32 g (25.0 mol) of 1-(2-chloro-3-bromo-5-nitrophenyl)-1-propanol were dropwise added to 25 ml of chloroform under cooling with ice in this order. The obtained mixture was stirred as such for 40 minutes, followed by the addition of a saturated aqueous solution of sodium hydrogen carbonate. The obtained mixture was stirred for 30 minutes and left standing to cause liquid-liquid separation. The chloroform phase was separated. The aqueous phase was further extracted with ethyl acetate and the ethyl acetate phase was washed with a saturated brine. The resulting ethyl acetate phase and the above chloroform phase were combined, dried and distilled to remove the solvent. The obtained residue was purified by silica gel column chromatography to give 6.64 g of the title compound (yield: 90%).
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.09(3H, t, J=7.5Hz), 1.78-2.12(2H, m), 5.78(1H, ddd, J=47.1, 7.9, 3.5Hz), 8.33(1H, d, J=2.7Hz), 8.48(1H, d, J=2.7Hz).

Example 230 Synthesis of 3-bromo-4-chloro-5-(1-fluoropropyl)aniline

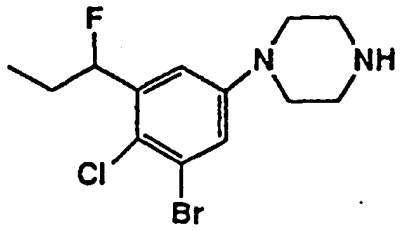
[0318]



[0319] 6.54 g (22.1 mmol) of 3-bromo-4-chloro-5-(l-fluoropropyl)-1-nitrobenzene was dissolved in a solvent mixture comprising 30 ml of methanol and 90 ml of acetonitrile, followed by the addition of 120 ml of a 20% solution of titanium trichloride in diluted hydrochloric acid under a nitrogen stream under cooling with ice. The obtained mixture was stirred at room temperature for 3 hours and then poured into water. The resulting mixture was extracted with ethyl acetate. The ethyl acetate phase was washed with a saturated aqueous solution of sodium hydrogen carbonate and a saturated brine successively, dried and distilled to remove the solvent. The residue was purified by silica gel column chromatography to give 5.04 g of the title compound (yield: 86%).
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.03(3H, t, J=7.5Hz), 1.7-2.1(2H, m), 3.77(2H, brs), 5.66(1H, ddd, J=47.4, 7.9, 3.6Hz), 6.74(1H, d, J=2.7Hz), 6.91(1H, d, J=2.7Hz).
MS m/z: 267[M^+], 265[M^+].

Example 231 Synthesis of 1-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpeperazine

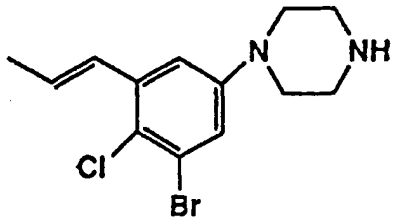
[0320]



[0321] 1.81 g (6.79 mmol) of 3-bromo-4-chloro-5-(1-fluoropropyl)aniline and 1.28 g (7.17 mmol) of bis(2-chloroethyl) amine hydrochloride were suspended in 6 ml of 1,2-dichlorobenzene. The obtained suspension was heated on an oil bath of 153°C under a nitrogen stream for 11 hours, cooled, adjusted to pH8 with a 2N aqueous solution of sodium hydroxide and extracted with ethyl acetate. The ethyl acetate phase was washed with a saturated brine, dried and distilled to remove the solvent. The obtained residue was purified by silica gel column chromatography to give 1.25 g (yield: 55%) of the title compound and 0.50 g (yield: 23%) of (E)-1-[3-bromo-4-chloro-5-(1-propenyl)]phenylpiperazine.

(E)-1-[3-Bromo-4-chloro-5-(1-propenyl)]phenylpiperazine

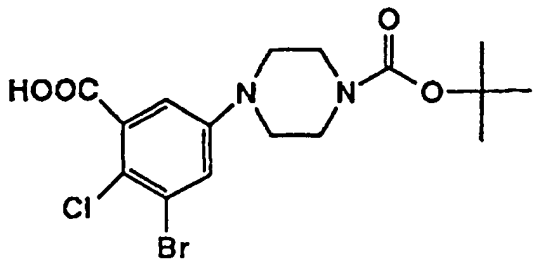
[0322]



^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.91(3H, dd, J=6.8, 1.8Hz), 3.66(1H, br), 6.68(1H, dq, J=15.7Hz, 6.8Hz), 6.72(1H, dd, J=15.7, 1.8Hz), 6.73(1H, d, J=2.7Hz), 6.85(1H, d, J=2.7Hz).
MS m/z: 317[MH]$^+$, 315[MH]$^+$.

Example 232 Synthesis of 1-(t-butoxycarbonyl)-4-(3-bromo-4-chloro-5-carboxy)phenylpiperazine

[0323]

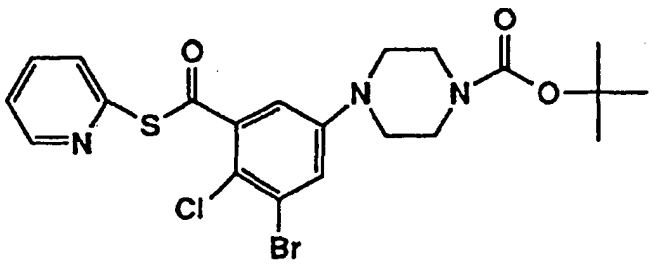


[0324] 20 ml of water, 150 ml of ethanol and 61 ml of a 2N aqueous solution of sodium hydroxide were added to 5.2 g (13.56 mmol) of 1-(3-bromo-4-chloro-5-ethoxycarbonyl)phenylpiperazine hydrochloride, followed by the addition of a solution of 5.29 g (2 equivalents) of di(t-butyl) dicarbonate [Boc_2O] in 25 ml of ethanol under cooling with ice. The

obtained mixture was freed from insolubles by filtration and distilled to remove the solvent, followed by the addition of 23 ml of 2N hydrochloric acid under cooling with ice. The obtained mixture was extracted with ethyl acetate. The ethyl acetate phase was dried and distilled to remove the solvent. Isopropyl ether was added to the obtained residue to precipitate a crystal. This crystal was recovered by filtration to give 4.64 g of the title compound (yield: 82%).
m.p.; 183~184.5°C (dec.)
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.48(9H, s), 3.17(4H, m), 3.58(4H, m), 4.2(1H, br), 7.30(1H, d, J=2.9Hz), 7.36(1H, d, J=2.9Hz).
MS m/z: 420[M$^+$], 418[M$^+$].

Example 233 Synthesis of 1-(t-butoxycarbonyl)-4-[3-bromo-4-chloro-5-(2-pyridylthio)carbonyl]phenylpiperazine

[0325]



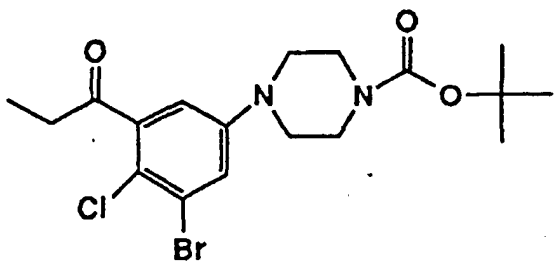
[0326] 1.06 ml (13.7 mmol) of N,N-dimethylformamide (hereinafter abbreviated to "DMF") and 0.99 ml (13.6 mmol) of thionyl chloride were added to 20 ml of tetrahydrofuran (hereinafter abbreviated to "THF"), followed by stirring at room temperature for at least 30 minutes. A solution of 5 g (11.9 mmol) of 1-(t-butoxycarbonyl)-4-(3-bromo-4-chloro-5-carboxy)-phenylpiperazine in 25 ml of THF was dropwise added to the mixture prepared above under cooling with ice, followed by stirring at 50°C for one hour. A solution of 2.07 g (18.6 mmol) of 2-mercaptopyridine and 5.2 ml (37.3 mmol) of triethylamine in 30 ml of THF was dropwise added to the resulting mixture under cooling with ice. The obtained mixture was stirred at room temperature for about one hour and then poured into ice-water. The resulting mixture was extracted with ethyl acetate. The organic phase was washed with a 1N aqueous solution of sodium hydroxide and a saturated brine, dried and distilled to remove the solvent. Isopropyl ether was added to the residue to precipitate a crystal. This crystal was recovered by filtration to give 5.61 g of the title compound (yield: 92%).

Example 234 Synthesis of 1-(t-butoxycarbonyl)-4-[3-bromo-4-chloro-5-(2-pyridylthio)carbonyl]phenylpiperazine

[0327] 5 g (11.9 mmol) of 1-(t-Butoxycarbonyl)-4-(3-bromo-4-chloro-5-carboxy)phenylpiperazine and 3.5 ml (25.1 mmol) of triethylamine were dissolved in 20 ml of THF. 30 ml of a solution of 2.7 ml (13.0 mmol) of diphenylphosphoric chloride in THF was dropwise added to the solution prepared above under cooling with ice, followed by stirring at room temperature for one hour. A solution of 1.51 g (1.14 equivalents) of 2-mercaptopyridine in 30 ml of THF was dropwise added to the resulting mixture under cooling with ice. The obtained mixture was stirred at 50°C for one hour and then poured into ice-water. The resulting mixture was extracted with ethyl acetate. The organic phase was washed with a 1N aqueous solution of sodium hydroxide and a saturated brine, dried and distilled to remove the solvent. Isopropyl ether was added to the residue to precipitate a crystal. This crystal was recovered by filtration to give 5.93 g of the title compound (yield: 97%).
m.p.; 156-157°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.48(9H, s), 3.19(4H, m), 3.58(4H, m), 7.15(1H, d, J=2.9Hz), 7.24(1H, d, J=2.9Hz), 7.35(1H, ddd, J=7.3, 4.8, 1.5Hz), 7.77(1H, ddd, J=7.9, 1.5, 0.9Hz), 7.82(1H, ddd, J=7.9, 7.3, 1.8Hz), 8.67(1H, ddd, J=4.8, 1.8, 0.9Hz).
MS m/z: 514[MH]$^+$, 512[MH]$^+$.

Example 235 Synthesis of 1-(t-butoxycarbonyl)-4-(3-bromo-4-chloro-5-propionyl)phenylpiperazine

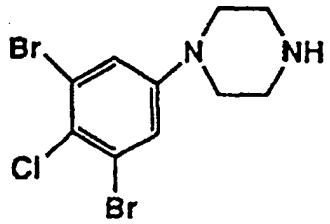
[0328]



[0329] 4.5 g (8.78 mmol) of 1-(t-butoxycarbonyl)-4-[3-bromo-4-chloro-5-(2-pyridylthio)carbonyl]phenylpiperazine was dissolved in 50 ml of THF. 9.7 ml of a 1M solution of ethylmagnesium bromide in THF was dropwise added to the obtained solution in 30 minutes, followed by the addition of a saturated aqueous solution of ammonium chloride and water in this order. The resulting mixture was extracted with ethyl acetate. The organic phase was washed with a 1N aqueous solution of sodium hydroxide and a saturated brine, dried and distilled to remove the solvent. The residue was purified by silica gel column chromatography (with ethyl acetate/hexane) to give 2.28 g of the title compound (yield: 60%).
m.p.; 119~122.5°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.20(3H, t, J=7.3Hz), 1.48(9H, s), 2.91(2H, q, J=7.3Hz), 3.15(4H, m), 3.57(4H, m), 6.72(1H, d, J=2.9Hz), 7.19(1H, d, J=2.9Hz).
MS m/z: 432[M^+], 430[M^+].

Example 236 Synthesis of 1-(3,5-dibromo-4-chloro)-phenylpiperazine

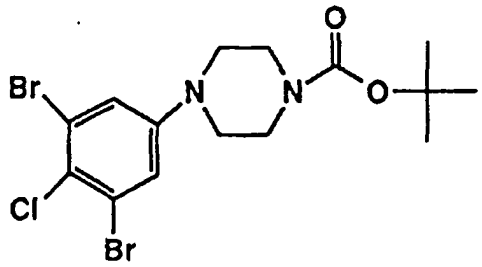
[0330]



[0331] 10.0 g (35 mmol) 3,5-dibromo-4-chloroaniline (CAS registration No. 35754-04-2) and 15.6 g (87.5 mmol) of bis(2-chloroethyl)amine hydrochloride were suspended in 120 ml of 1,2-dichlorobenzene. The obtained suspension was heated on an oil bath of 180°C under a nitrogen stream for 8 hours. 300 ml of ethyl acetate was added to the resulting mixture to form a precipitate. This precipitate was recovered by filtration, washed with ethyl acetate and suspended in 500 ml of methanol. The obtained suspension was heated under reflux, freed from insolubles by filtration, and distilled to remove the solvent. The crystal thus precipitated was recovered by filtration to give 13.7 g of the title compound (yield: 100%).
m.p.; over 270°C
^{1}H-NMR(400MHz, DMSO-d_6); δ(ppm) 3.14(4H, m), 3.46(4H, m), 7.38(2H, s).
MS m/z: 357[$MH]^+$, 355[$MH]^+$, 353[$MH]^+$.

Example 237 Synthesis of 1-(t-butoxycarbonyl)-4-(3,5dibromo-4-chloro)phenylpiperazine

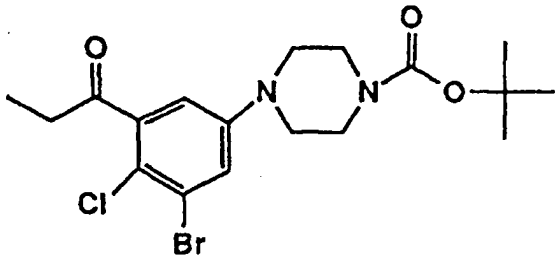
[0332]



[0333] 13.7 g (35 mmol) of 1-(3,5-dibromo-4-chloro)-phenylpiperazine was suspended in 200 ml of acetonitrile, followed by the dropwise addition of 14.4 ml (70 mmol) of triethylamine under cooling with ice. A solution of 11.1 g (42 mmol) of di(t-butyl) dicarbonate in 15 ml of acetonitrile was dropwise added to the resulting mixture under cooling with ice in 10 minutes. The obtained mixture was stirred at room temperature for 15 hours, followed by the addition of water. The resulting mixture was extracted with ethyl acetate. The organic phase was washed with water, dried and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (with ethyl ether/hexane) to give 17.8 g of the title compound as a colorless crystal (yield: 83.3%).
m.p.; 149-151°C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.48(9H, s), 3.13(4H, m), 3.57(4H, m), 7.10(2H, s).
MS m/z: 456[M]$^+$, 454[M]$^+$, 452[M]$^+$.

Example 238 Synthesis of 1-(t-butoxycarbonyl)-4-(3-bromo-4-chloro-5-propionyl)phenylpiperazine

[0334]

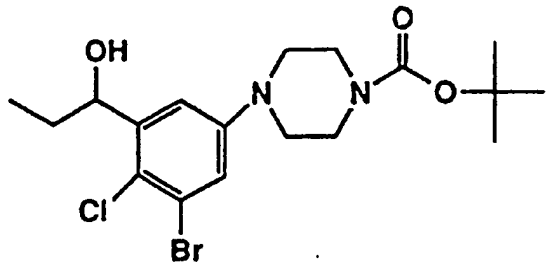


[0335] 3.8 ml of a 1.66M solution of n-butyllithium in n-hexane was dropwise added to a solution of 2.5 g (5.5 mmol) of 1-(t-butoxycarbonyl)-4-(3,5-dibromo-4-chloro)phenylpiperazine in 10 ml of THF in about 5 minutes at -100°C. Then, a solution of 860 mg (6.6 mmol) of propionic anhydride in 2.5 ml of THF was dropwise added to the above-prepared mixture at -100°C in about 3 minutes. The obtained mixture was stirred as such for one hour (during this stirring, the temperature rose from -100°C to -20°C). A saturated aqueous solution of ammonium chloride was added to the resulting mixture, followed by extraction with ethyl acetate. The organic phase was washed with water and a saturated brine, dried and distilled to remove the solvent. The residue was purified by silica gel column chromatography (with ethyl acetate/n-hexane) to give 1.55 g of the title compound (yield: 65%).

[0336] 15 ml of isopropanol was added to the above product. The product was dissolved in the isopropanol by heating and the obtained solution was stirred under cooling with ice for one hour to precipitate a crystal. This crystal was recovered by filtration to give 1.0 g of the title compound as a crystal (yield: 42.1%).
m.p.; 121~123° C
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 1.20(3H, t, J=7.3Hz), 1.48(9H, s), 2.91(2H, q, J=7.3Hz), 3.15(4H, m), 3.57(4H, m), 6.72(1H, d, J=2.9Hz), 7.19(1H, d, J=2.9Hz).

Example 239 Synthesis of 1-(t-butoxycarbonyl)-4-[3-bromo-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine

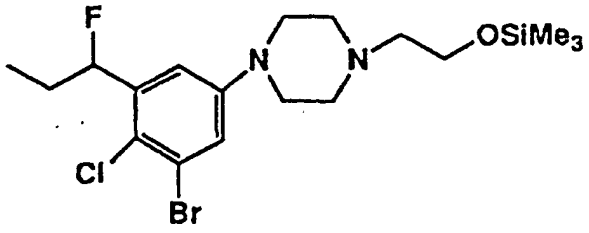
[0337]



[0338] 0.8 ml (1.2 equivalents) of a 1.66 M solution of n-butyllithium in n-hexane was dropwise added to a solution of 500 g (1.1 mmol) of 1-(t-butoxycarbonyl)-4-(3,5-dibromo-4-chloro)phenylpiperazine in 10 ml of THF at -76°C in about 4 minutes, followed by the dropwise addition of a solution of 77 mg (1.3 mmol) of propionaldehyde in 0.5 ml of THF at -76°C in about 2 minutes. The obtained mixture was stirred as such for one hour (during this stirring, the temperature rose from -76°C to -10°C). A saturated aqueous solution of ammonium chloride was added to the resulting mixture, followed by extraction with ethyl acetate. The organic phase was washed with water and a saturated brine, dried and distilled to remove the solvent. The residue was purified by silica gel column chromatography (with ethyl acetate/n-hexane) to give 0.31 g of the title compound as a colorless oil (yield: 65%).
^{1}H-NMR(400MHz, DMSO-d_6); δ(ppm) 1.01(3H, t, J=7.6Hz), 1.48(9H, s), 1.6-1.9(2H, m), 3.15(4H, m), 3.58(4H, m), 5.03(1H, m), 6.07(1H, d, J=2.9Hz), 7.10(1H, d, J=2.9Hz).
MS m/z: 434[M]$^+$, 432[M]$^+$.

Example 240 Synthesis of 1-(2-trimethylsilyloxyethyl)-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]-phenylpiperazine

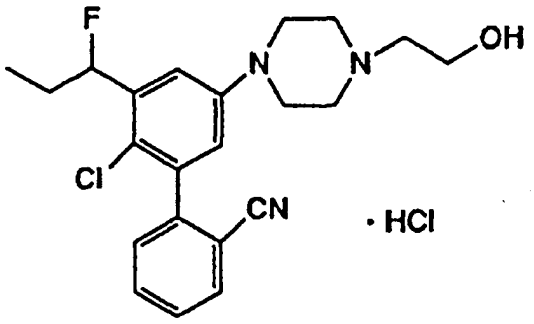
[0339]



[0340] 500 mg (1.05 mmol) of 1-(2-hydroxyethyl)-4-[3-bromo-4-chloro-5-(l-fluoropropyl)]phenylpiperazine methanesulfonate was suspended in 5 ml of ethyl acetate, followed by the addition of 0.35 ml (2.56 mmol) of triethylamine under cooling with ice. A solution of 0.16 ml (1.26 mmol) of trimethylsilyl chloride in 1 ml of ethyl acetate was dropwise added to the resulting mixture while stirring the mixture under cooling with ice. The obtained mixture was stirred at room temperature for 1.5 hours, followed by the addition of 5 ml of n-hexane. The obtained mixture was filtered to remove insolubles and the filtrate was concentrated under reduced pressure to give 0.51 g of the title compound. This product was used in the following reaction without any additional purification.
^{1}H-NMR(400MHz, $CDCl_3$); δ(ppm) 0.13(9H, s), 1.04(3H, t, J=7.3Hz), 1.7-2.0(2H, m), 2.58(2H, t, J=6.2Hz), 2.66(4H, m), 3.19(4H, m), 3.75(2H, J=6.2Hz), 5.69(1H, ddd, J=47.5, 7.9, 3,7Hz), 6.95(1H, d, J=2.9Hz), 7.09(1H, d, J=2.9Hz).

Example 241 Synthesis of 1-(2-hydroxyethyl)-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine hydrochloride

[0341]

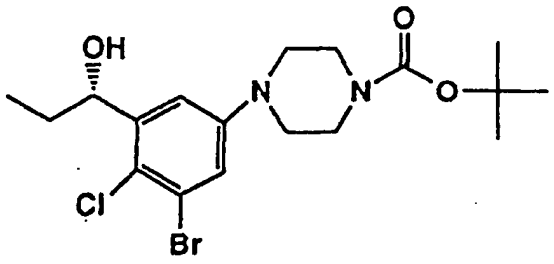


[0342] 1-(2-Trimethylsilyloxyethyl)-4-[3-bromo-4-chloro-5-(1-fluoropropyl)]phenylpiperazine was dissolved in 4 ml of DMF, followed by the addition of 334 mg (1.58 mmol) of potassium phosphate and 61 mg (0.05 mmol) of tetrakis (triphenylphosphine)palladium (0). A solution of 236 mg (1.26 mmol) of 2-(1,3,2-dioxaborinan-2-yl)benzonitrile in 3 ml of DMF was dropwise added to the resulting mixture at 100°C in 30 minutes. The obtained mixture was stirred as such at 100°C for 30 minutes and cooled, followed by the addition of water. The resulting mixture was extracted with ethyl acetate. The organic phase was washed with water and a saturated brine, dried and distilled to remove the solvent, giving 0.52 g of a residue.

[0343] This residue was dissolved in 1 ml of ethanol, followed by the dropwise addition of 0.57 g of a 10% solution of hydrochloric acid in ethanol under cooling with ice. The obtained mixture was stirred at 4°C for 20 hours to give a precipitate. The precipitate was recovered by filtration and dried to give 0.39 g of the title compound (yield: 83.9%).

Example 242 Synthesis of 1-(t-butoxycarbonyl)-4-(3-bromo-4-chloro-5-[1-(S)-hydroxypropyl]}phenylpiperazine

[0344]



[0345] 55.8 g (173 mmol) of (-)-Dip-chloride [CAS registration No. 85116-37-6] was added to a solution of 30.0 g (69.7 mmol) of 1-(t-butoxycarbonyl)-4-(3-bromo-4-chloro-5-propionyl)phenylpiperazine in 450 ml of THF. The obtained mixture was stirred at room temperature for 24 hours. Water and ethyl acetate were added to the reaction mixture to conduct partition. The organic phase was washed with water and a brine, dried and distilled to remove the solvent. The residue was purified by silica gel chromatography to give 27.2 g of the title compound (yield: 90%, optical purity; 94 %ee).

(Method for the determination of optical purity)

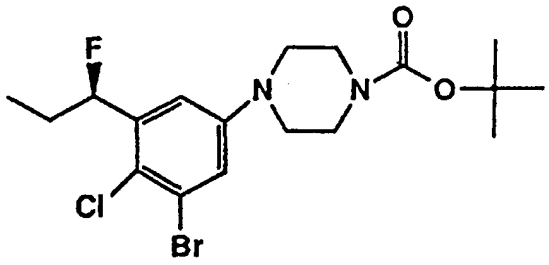
[0346] A proper amount of a sample was deprotected with trifluoroacetic acid and treated with carbobenzoxy chloride (hereinafter abbreviated to "Z-Cl") to form an N-Z derivative, which was used as a test sample.

(Conditions of determination)	
stationary phase	CHIRALPAK AD (a product of Daicel Chemical Industries, Ltd.) Φ 4.6 × 250 mm
mobile phase	ethanol (0.5 ml/min.)
detector	UV detector, at 254nm

(Retention time)	S isomer	23 to 24 min.
	R isomer	28 to 30 min.

Example 243 Synthesis of 1-(t-butoxycarbonyl)-4-{3-bromo-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine

[0347]



[0348] 19.4 g (41.5 mmol) of hexafluoropropenediethylamine was dropwise added to a solution of 18.0 g (41.5 mmol, 94 %ee) of 1-(t-butoxycarbonyl)-4-{3-bromo-4-chloro-5-[1-(S)-hydroxypropyl]}phenylpiperazine in 90 ml of chloroform under cooling with ice. The obtained mixture was stirred as such for 2 hours. 90 ml of carbon tetrachloride was added to the reaction mixture to precipitate a salt, which was filtered out. 80 ml of water was added to the filtrate to conduct partition. The organic phase was washed with a brine and distilled to remove the solvent. The obtained residue was purified by silica gel chromatography to give 11.2 g of the title compound (yield: 62%, optical purity: 55 %ee).

(Method for the determination of optical purity)

[0349] The optical purity was determined under the same conditions as those described above.

(Retention time)	S isomer	17 to 19 min.
	R isomer	20 to 21 min.

Example 244 Synthesis of 1-(t-butoxycarbonyl)-4-{3-bromo-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine

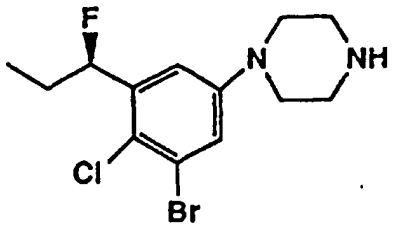
[0350] A solution of 15.0 g (34.6 mmol) of 1-(t-butoxycarbonyl)-4-{3-bromo-4-chloro-5-[1-(S)-hydroxypropyl]}phenylpiperazine in 30 ml of methylene chloride was dropwise added to a solution of 6.15 g (38.0 mmol) of diethylaminosulfur trifluoride in 15 ml of methylene chloride at -70°C. The resulting mixture was stirred as such for one hour, brought to room temperature and neutralized with a saturated aqueous solution of sodium hydrogen carbonate. The resulting mixture was extracted with methylene chloride. The organic phase was washed with water and distilled to remove the solvent. The residue was purified by silica gel chromatography to give 12.5 g of the title compound (yield: 83%, optical purity: 34 %ee).

(Method for the determination of optical purity)

[0351] The opticl purity was determined under the same conditions as those described above.

Example 245 Synthesis of 1-{3-bromo-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine

[0352]



[0353] A solution of 6.75 g (68.8 mmol) of concentrated sulfuric acid in 25 ml of ethanol was added to a solution of 15.0 g (34.4 mmol) of 1-(t-butoxycarbonyl)-4-{3-bromo-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine in 50 ml of ethanol. The obtained mixture was stirred at 50°C for 3 hours and then concentrated under reduced pressure. Ethyl acetate and a 5N aqueous solution of sodium hydroxide were added to the obtained residue to conduct partition. The organic phase was washed with a brine and distilled to remove the solvent, giving 10.3 g of the title compound (yield: 89%).

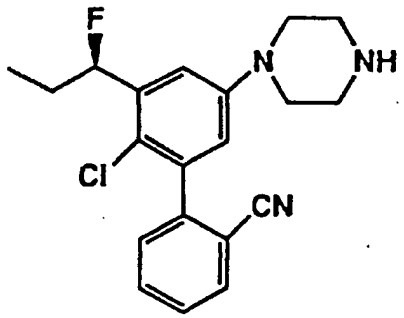
(Method for the determination of optical purity)

[0354] The optical purity was determined under the same conditions as those described above.

(Retention time)	S isomer	17 to 19 min.
	R isomer	20 to 21 min.

Example 246 Synthesis of 1-{3-(2-cyanophenyl)-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine

[0355]



[0356] 14.0 g (41.7 mmol) of 1-{3-bromo-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine, 2.4 g (2.08 mmol) of tetrakis(triphenylphosphine)palladium and 13.3 g (62.6 mmol) of anhydrous tripotassium phosphate were suspended in 28 ml of DMF, followed by the dropwise addition of a solution of 9.5 g (50.0 mmol) of 2-(1,3,2-dioxaborinan-2-yl)benzonitrile in 19 ml of DMF at 100°C. The obtained mixture was stirred as such for 3 hours and then cooled to room temperature. Water and ethyl acetate were added to the resulting mixture to conduct-partition. The organic phase was washed with a brine and distilled to remove the solvent. The obtained residue was purified by silica gel chromatography to give 10.6 g of the title compound (yield: 71%).

(Method for the determination of optical purity)

[0357] The optical purity was determined under the same conditions as those described above.

(Retention time)	S isomer	10 to 12 min.
	R isomer	12 to 14 min.

Example 247 Optical purification of 1-{3-(2-cyanophenyl)-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine

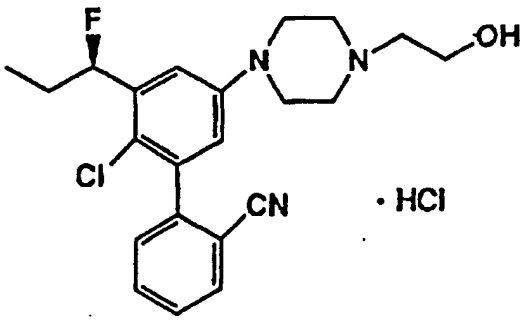
[0358] A solution of 4.0 g (10.5 mmol) of (+)-di-p-toluoyl-D-tartaric acid in 100 ml of methanol was added to a solution of 10.0 g (27.9 mmol, 55 %ee) of the title compound prepared in the above Example in 300 ml of methanol at room temperature. After the precipitation of a crystal, the resulting mixture was stirred under cooling with ice for one hour and then filtered to recover the crystal. The crystal was neutralized with a 5N aqueous solution of sodium hydroxide and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with a brine and distilled to remove the solvent, giving 6.4 g of the title compound as an optically active substance (yield: 64%, optical purity: 90 %ee).

(Method for the determination of optical purity)

[0359] The optical purity was determined under the same conditions as those described above.

Example 248 Synthesis of 1-(2-hydroxyethyl)-4-{3-(2-cyanophenyl)-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine hydrochloride

[0360]



[0361] 2.8 g (28.0 mmol) of triethylamine and 3.5 g (28.0 mmol) of 2-bromoethanol were added to a solution of 5.0 g (14.0 mmol) of the optically active 1-{3-(2-cyanophenyl)-4-chloro-5-[1-(R)-fluoropropyl]}phenylpiperazine prepared in the above Example in 10 ml of DMF. The obtained mixture was stirred at 50°C for 3 hours and then cooled to room temperature. Water and toluene were added to the resulting mixture to conduct partition. The organic phase was washed with water and distilled to remove the solvent, giving 5.5 g of the title compound as a crude product (yield: 98%).

[0362] A solution of 5.5 g (13.7 mmol) of this crude product in 55 ml of 3% methanol/ethanol was dropwise added to a solution of 1.52 g (15.1 mmol) of concentrated hydrochloric acid in 27.5 ml of ethanol at 60°C. After the completion of the dropwise addition, the resulting mixture was stirred while cooled by allowing to stand. After the precipitation of a crystal, the resulting mixture was further stirred under cooling with ice for one hour and filtered to recover the crystal. Thus, 5.2 g of the title compound (i.e., a hydrochloride) was obtained (yield: 86%).

[0363] The compounds of the present invention were subjected to each of serotonin S_2 receptor binding test, dopamine D_2 receptor binding test and adrenergic α_1 receptor binding test. The methods and results, which exhibit the effect of the present invention, will be given hereinafter.

(Method)

1. Reagent

[0364] The following reagents were used in this test.

(1) Methylsergide maleate (a product of RBI)
(2) Spiperone (a product of Sigma)
(3) Phentolamine (a product of Sigma) Further, the following reagents (all of which are products of NEN) were used as radioisotope-labeled compounds.
(4) Ketanserin hydrochloride [ethylene-^{3}H]
(5) Spiperone [benzene ring-^{3}H]
(6) Prazosin [7-methoxy-^{3}H]

[0365] These reagents and samples were each dissolved in 10% ethanol before use. Among them, water-insoluble compounds were each dissolved in ethanol and the obtained solution was diluted with distilled water to an ethanol concentration of 10%. Further, Methylsergide maleate was used in a state dissolved in distilled water.

2. Animal

[0366] SD rats aged 6 to 8 weeks were used.

3. Preparation of receptor sources

[0367] SD rats were each slaughtered with a guillotine to extirpate its cerebrum. The cortex and corpus striatum were separated from the cerebrum. The former was used in serotonin S_2 receptor binding test and adrenergic α_1 receptor binding test, while the latter was used in dopamine D_2 receptor binding test.

[0368] The cortex was homogenized in a 0.32 M sucrose solution in an amount ten times the wet weight of the cortex by the use of a teflon glass homogenizer and the resulting mixture was cetrifuged at 10,000 x G for 20 minutes. The obtained sediment was suspended in 50 mM Tris hydrochloride (pH 7.4) in an amount ten times the initial wet weight of the cortex by the use of a histocothrom, and the obtained suspension was centrifuged at 10,000 × G for 20 minutes. This operation was repeated twice. The obtained sediment was suspended in 50 mM Tris hydrochloride (pH 7.4) in an amount 20 times the initial wet weight of the cortex by the use of a histocothrom. The suspension thus prepared was used as a receptor fraction. This receptor fraction was stored at -80°C until use.

[0369] On the other hand, the corpus striatum was homogenized in a 0.32 M sucrose solution in an amount ten times the wet weight of the corpus striatum by the use of a teflon glass homogenizer and the obtained mixture was centrifuged at 1,000 × G for 20 minutes. The obtained supernatant was centrifuged at 10,000 × G for 20 minutes. The obtained sediments were suspended together in 50 mM Tris hydrochloride (pH 7.4) in an amount ten times the initial wet weight of the corpus striatum by the use of a histocothrom, and the obtained suspension was centrifuged at 10,000 × G for 20 minutes. This operation was repeated thrice. The resulting sediment was suspended in 50 mM Krebs-Tris (pH 7.4) in an amount 100 times the initial wet weight of the corpus striatum by the use of a histocothrom. The obtained suspension was used as a receptor fraction. This receptor fraction was stored at -80°C until use.

4. [^{3}H] Ketanserin binding test

[0370] The receptor fraction prepared from the cortex was molten and suspended by the use of a histocothrom. The resulting suspension was incubated together with 1nM-[^{3}H] Ketanserin at 37°C for 15 minutes. The resulting reaction system was filtered through a Whatman GF/B glass filter with an MR-30R type cell harvester mfd. by Blandel. The resulting filter was washed twice with 5 ml of 50 mM Tris hydrochloride (pH 7.4) cooled with ice and the radioactivity of the Ketanserin bound the receptor was determined by the use of a liquid scintillation counter with 5 ml of ACS II. The binding detected in the presence of 1 µl of Methylsergide was regarded as nonspecific binding.

[0371] Each IC_{50} value was calculated by the probit method and each Ki value was determined by the following formula:

$$Ki = \frac{IC_{50}}{1+C/Kd}$$

[0372] In the above formula, C represents the concentration of radioligand, and Kd represents the affinity of radioligand for the receptor as determined by the Scatchard analysis.

5. [^{3}H] Spiperone binding test

[0373] This test was conducted in the same manner as that of the binding test of [^{3}H] Ketanserin except that the

receptor fraction prepared from the corpus striatum was molten and suspended with a histocothrom, and the obtained suspension was incubated together with 1 nM-[^{3}H] Spiperone at room temperature for 60 minutes and that the binding detected in the presence of 10 µl of Spiperone was regarded as nonspecific binding.

6. [^{3}H] Prazosin binding test

[0374] This test was conducted in the same manner as that of the binding test of [^{3}H] Ketanserin except that the receptor fraction prepared from the cortex was molten and suspended with a histocothrom, and the obtained suspension was incubated together with 1 nM-[^{3}H] Prazosin at room temperature for 60 minutes and that the binding detected in the presence of 10 µl of Phentolamine was regarded as nonspecific binding.

(Result)

[0375] The results of the evaluation of compounds according to the present invention are given in Tables 1 to 8.

Table 1

Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
13	24.9	4.05	404
17	374	>100	550
18	6.15	0.75	53.7
19	1.95	0.64	81.6
20	6.11	2.82	313.6
21	14.4	1.85	418
22	19.2	2.84	809
23	51.2	7.22	-
24	40.9	3.60	537
25	8.27	2.40	>1000
26	21.6	2.67	>1000
27	10.9	11.2	455
28	5.67	1.60	50.8
29	4.86	1.19	50.1
30	2.24	0.86	92.5
31	12.4	0.69	36.1
32	3.36	0.38	19.5
33	6.46	2.02	86.9
34	7.77	0.37	25.8
35	3.37	0.50	17.0
36	4.04	1.26	25.3
40	3.64	9.25	>1000

Table 2

Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
45	192	26.9	183
46	2.16	9.78	>1000
47	5.72	12.9	>1000
48	4.32	25.8	>1000
49	20.1	6.09	>1000
50	17.7	9.14	>1000
51	164	27.2	>1000

Table 2 (continued)

Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
52	21.6	0.99	>1000
53	12.4	6.73	>1000
54	37.5	6.06	>1000
55	113.04	3.10	>1000

Table 3

Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
56	212	111	503
57	>1000	>1000	>1000
58	>1000	>1000	290
59	36.7	47.0	301
60	>1000	>1000	>1000
61	>1000	>1000	>1000
62	>1000	>1000	>1000
63	703	>1000	>1000
64	284	384	459
65	26.6	6.60	79.0
66	65.9	18.3	127
67	>1000	>1000	687
68	32.0	35.1	195
69	67.1	171	321
70	128	41.9	322
71	90.9	14.7	131
72	108	50.3	270
73	635	577	332
74	374	>1000	>1000
75	486	>1000	>1000
76	145	50.1	112
77	24.3	40.0	182
78	33.2	4.22	74.8
79	192	28.5	69.8
80	177	810	>1000

Table 4

Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
81	241	38.3	>1000
82	10.7	39.1	723
83	84.5	485	>1000
84	66.2	44.6	>1000
85	>1000	>1000	>1000
86	29.4	10.5	>1000
87	283	135	>1000
88	8.33	7.35	493

Table 4 (continued)

Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
89	310	44.6	>1000
90	685	263	>1000
91	37.1	7.34	323
92	1.14	2.71	942
93	1.31	28.0	719
94	109	13.8	600
95	40.9	104	279
96	35.3	1.33	>1000
97	247	>1000	>1000
98	19.3	64.5	>1000
99	170	2.93	>1000
100	827	82.7	846
101	262	118	>1000
102	>1000	>1000	525
103	6.65	101	>1000
104	24.5	70.1	>1000
105	5.21	30.2	620
106	380	44.0	>1000
107	>1000	429	>1000
108	4.00	162	408
109	230	>1000	>1000
110	>1000	>1000	>1000

Table 5

Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
111	58.0	41.9	210
112	7.00	972	>1000
113	21.1	8.73	28.9
114	151	165	569
115	212	81.4	>1000
116	39.5	9.65	>1000
117	148	49.6	334
118	468	149	>1000
119	34.9	35.8	>1000
120	17.4	0.36	77.6
121	168	11.0	308
122	123	45.9	68.1
123	17.9	27.0	>1000
124	>1000	99.2	>1000
125	1.49	101	>1000
126	27.3	54.6	>1000
127	11.4	1.04	65.9
128	1.16	46.1	>1000
129	34.9	1.86	39.8
130	58.0	29.7	70.4

Table 5 (continued)

Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
131	20.8	3.30	>1000
132	392	281	>1000
133	9.02	28.7	>1000
134	30.3	59.7	>1000
135	16.0	42.1	>1000
136	89.0	14.2	472
137	144	0.64	312
138	25.0	2.89	9.33
139	5.38	2.34	68.7
140	26.2	2.97	95.5

Table 6

Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
141	92.7	24.9	>1000
142	20.5	1.77	653
143	156	16.9	>1000
144	15.7	0.81	67.4
145	72.5	8.28	>1000
146	13.2	0.83	349
147	15.1	0.45	33.2
148	22.4	12.1	278
149	11.6	6.24	27.2
150	97.1	7.98	>1000
151	27.7	3.52	>1000
153	4.19	1.53	68.7
154	153	2.59	>1000
155	179.6	41.0	845.0
156	29.0	1.39	513.4
157	74.4	7.26	>1000
158	124	12.4	>1000
159	8.81	3.93	596
160	14.8	13.6	>1000
161	22.5	9.80	776
162	6.15	0.75	53.7
163	63.6	10.2	195
164	12.0	1.62	>1000
165	6.10	0.74	>1000
166	5.42	1.42	>1000
167	23.8	45.4	>1000
168	180	31.9	>1000
169	108	41.8	>1000
170	2.77	34.2	>1000

Table 7

Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
171	2.74	86.7	>1000
172	30.3	48.9	>1000
173	>1000	19.2	>1000
174	48.7	31.8	>1000
175	>100	29.32	>1000
176	178	>100	>1000
177	>100	>100	>1000
178	12.2	7.30	>1000
179	6.54	6.08	72.7
180	3.48	13.0	>100
181	0.50	26.2	>100
182	145	2.34	186
183	81.2	165	>1000
184	2.09	0.17	4.52
185	>100	0.58	>1000
186	4.29	2.96	>1000
187	38.2	0.54	7.80
188	47.8	1.33	19.0
189	>100	1.51	32.5
190	18.5	40.4	>1000
191	3.76	1.65	21.2
192	374	>100	550
193	1.61	19.3	585
194	4.45	0.83	>1000
195	5.75	70.6	>1000
196	13.2	5.52	744
197	8.86	1.40	31.4
198	1.06	12.1	62.7
199	63.2	51.5	-
200	-	-	-

Table 8

Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
201	3.17	19.7	12.9
202	6.33	90.5	-
203	54.8	-	-
204	187	14.4	-
205	51.2	2.83	-
206	4.29	1.06	47.8
207	81.1	240.3	>1000
208	16.1	3.46	2379
209	42.7	3.90	-
210	6.25	16.1	-
211	8.81	4.14	1024
212	1019	3.90	-

Table 8 (continued)

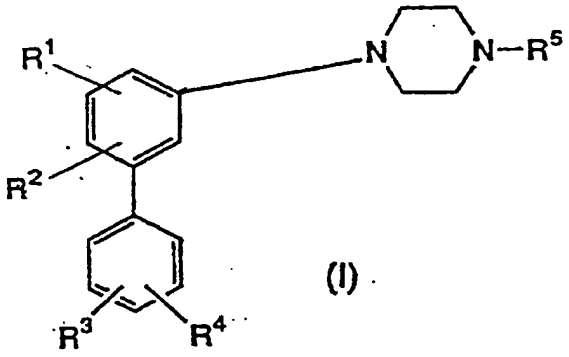
Ex.	Ki value (nM)		
	serotonin S_2 receptor	dopamine D_2 receptor	adrenergic α_1 receptor
213	10.3	14.3	236
214	3.78	5.15	51.7
215	15.3	2.28	-
216	79.0	11.3	-
217	25.5	3.57	-
218	30.1	5.39	-
219	151	5.54	-
220	37.9	1.25	1680
221	4.53	3.45	486
222	12.0	6.50	1040
223	1860	6.61	1510
risperidone	0.62	5.03	2.94

[0376] It can be understood from the results of the Tables 1 to 8 that the biphenyl derivative of the present invention exhibits excellent therapeutic and ameliorative effects on mental disorders such as cerebrovascular disorder, aggressive behavior due to senile dementia, mental excitation, poriomania, delirium, hallucination, hyperkinesia, schizophrenia, emotional disturbance, depression, neurosis, psychophysiologic disorder and anxiety neurosis.

[0377] The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

Claims

1. A biphenyl derivative represented by the following formula (I) or a pharmacologically acceptable salt thereof:



(I)

wherein R^1 represents a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a cyano group, a pyrrolidyl group, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a cyano C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, an amino C_1-C_6 alkyl group, a cycloalkyl group, a cycloalkylalkyl group, a C_1-C_6 alkoxyalkyl group, a heteroarylalkyl group, a halogenated heteroarylalkyl group, a C_1-C_6 acylalkyl group, a heteroarylalkoxyalkyl group, a cycloalkyloxyalkyl group, an aralkyloxyalkyl group, an alkenyloxyalkyl group, a C_1-C_6 alkoxycarbonylalkyl group, a C_1-C_6 alkoxyalkoxyalkyl group, an arylhydroxyalkyl group, a hydroxyheteroarylalkyl group, a cycloalkylalkoxyalkyl group, an alkenyl group, a halogenated alkenyl group, an alkynyl group, an aralkyl group, a halogenated aralkyl group, a hydroxyaralkyl group, a halogenated hydroxyiminoaralkyl group, a C_1-C_6 alkoxy group, a halogenated C_1-C_6 alkoxy group, a C_1-C_6 alkoxyalkoxy group, an aryl group, a hydroxyaryl group, a halogenated aryl group, a C_1-C_6 alkoxyaryl group, a heteroaryl group, a hydroxyheteroaryl group, a halogenated heteroaryl group, a C_1-C_6 alkoxyheteroaryl group, formyl group, a C_1-C_6 acyl group, an aromatic acyl group, a heteroaromatic acyl

group, an aralkylcarbonyl group, a cycloalkylalkylcarbonyl group, a heteroarylalkylcarbonyl group, a halogenated aralkylcarbonyl group, a C_1-C_6 alkoxycarbonyl group, an aryloxycarbonyl group, a C_1-C_6 alkylamino group, a C_1-C_6 alkylsulfonylamino group, a halogenated C_1-C_6 alkylsulfonylamino group, an arylsulfonylamino group, a halogenated arylsulfonylamino group, an aralkylsulfonyl amino group, a cycloether group, a C_1-C_6 cyclic acetal group, a C_1-C_6 cyclic thioacetal group, a C_1-C_6 alkylsulfinyl group, an arylsulfinyl group, an aralkylsulfinyl group, a heteroarylsulfinyl group, a C_1-C_6 alkylsulfonyl group, an arylsulfonyl group, an aralkylsulfonyl group, a heteroarylsulfonyl group, a cycloalkylsulfonyl group, an aminosulfonyl group, a C_1-C_6 alkylaminosulfonyl group, an arylaminosulfonyl group, a pyrrolidylsulfonyl group, a cycloalkylaminosulfonyl group, a halogenated C_1-C_6 alkylsulfonyl group, a halogenated aryloxy C_1-C_6 alkylsulfonyl group or a cyano C_1-C_6 alkylsulfonyl group;

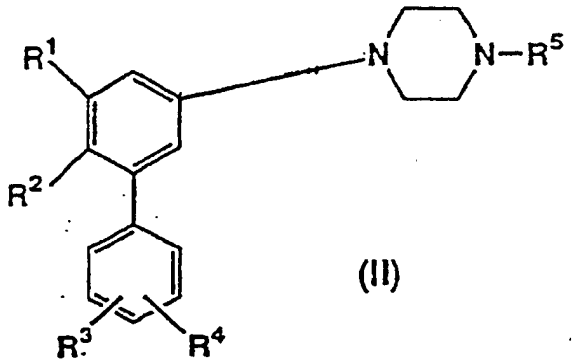
R^2 and R^3 may be the same or different from each other and each represents a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a C_1-C_6 alkoxyalkyl group, a C_1-C_6 alkoxy group or a halogenated C_1-C_6 alkoxy group;

R^4 represents a hydrogen atom, a halogen atom, a C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, a hydroxylminomethyl group or a formyl group;

R^5 represents a hydrogen atom, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, a heteroarylalkyl group, a C_1-C_6 alkoxycarbonyl group or an aryloxycarbonyl group;

provided that the biphenyl derivative is neither 1-[3-phenyl-4-methyl)-phenyl]-piperazine nor 1-methyl-4-[(3-phenyl-4-methyl)-phenyl]-piperazine; and provided that R^5 does not represent a hydrogen atom if R^1 and R^2 represent hydrogen atoms, R^3 represents a hydrogen atom, a halogen atom, or a hydroxyl group and if R^4 represents a hydrogen atom, a halogen atom or a formyl group. wherein the term heteroaryl group denotes a thienyl group, furanyl group, pyranyl group, imadazolyl group, thiazolyl group, pyridyl group or pyrazyl group; the term heteroarylalkyl group denotes a thienylmethyl group, furfuryl group, imidazolylmethyl group, thiazolylmethyl group, pyridylmethyl group or pyrazylmethyl group; the term halogenated heteroarylalkyl group denotes a heteroarylalkyl group as defined above in which at least one hydrogen atom is replaced by a halogen atom; and wherein the term aryl group denotes an unsubstituted aryl group, a tolyl group, a xylyl group, a methoxyphenyl group, a chlorophenyl group, a bromophenyl group, a fluorophenyl group, a nitrophenyl group or a cyanophenyl group.

2. The biphenyl derivative or the pharmacologically acceptable salt thereof as set forth in Claim 1, wherein the biphenyl derivative is represented by the following formula (II):



(II)

wherein R^1, R^2, R^3, R^4, and R^5 are each as defined above.

3. The biphenyl derivative or the pharmacologically acceptable salt thereof as set forth in Claim 1, wherein R^1 represents a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogenated C_1-C_6 alkoxy group, a C_1-C_6 alkoxyalkyl group, a C_1-C_6 alkoxyalkoxy group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group, a halogenated heteroarylalkyl group, a cyano C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, an amino C_1-C_6 alkyl group, a C_1-C_6 alkoxycarbonyl group, an aryloxycarbonyl group, a cyano group, a formyl group, a C_1-C_6 acyl group, an aralkylcarbonyl group, a cycloether group, an alkenyl group, an alkynyl group, a C_1-C_6 alkylsulfinyl group, a C_1-C_6 alkylsulfonyl group, a C_1-C_6 alkylaminosulfonyl group, an arylaminosulfonyl group, a C_1-C_6 alkylsulfonylamino group, a halogenated C_1-C_6 alkylsulfonylamino group or an arylsulfonylamino group;

R^2 and R^3 may be the same or different from each other and each represents a hydrogen atom, a halogen atom, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogenated C_1-C_6 alkoxy

group or a cyano group;

R^4 represents a hydrogen atom or a halogen atom;

R^5 represents a hydrogen atom, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, a C_1-C_6 alkoxycarbonyl group or an aryloxycarbonyl group.

4. The biphenyl derivative or the pharmacologically acceptable salt thereof as set forth in Claim 1, wherein R^1 is a halogenated C_1-C_6 alkyl group or a C_1-C_6 alkylsulfonylamino group; R^2 is a halogen atom or a C_1-C_6 alkoxy group; R^3 is a halogen atom, a C_1-C_6 alkyl group or a cyano group; R^4 is a hydrogen atom or a halogen atom; R^5 is a hydrogen atom, a C_1-C_6 alkyl group or a hydroxy C_1-C_6 alkyl group.

5. The biphenyl derivative or the pharmacologically acceptable salt thereof as set forth in Claim 1, which is a compound selected from the group consisting of

(1) 1-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(2) 1-(2-hydroxyethyl)-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(3) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-ethoxycarbonyl]phenylpiperazine,
(4) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-amino]-phenylpiperazine,
(5) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(6) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine,
(7) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-butanesulfonylamino]phenylpiperazine,
(8) 1-methyl-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(9) 1-ethyl-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(10) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(11) 1-(2-hydroxyethyl)-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(12) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(13) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(14) 1-(2-hydroxyethyl)-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(15) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(16) 1-methyl-4-(3-(2-tolyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine,
(17) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(18) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-butanesulfonylamino]phenylpiperazine,
(19) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine,
(20) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(21) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-butanesulfonylamino]phenylpiperazine,
(22) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine,
(23) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(24) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-butanesulfonylamino]phenylpiperazine,
(25) 1-ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonylamino]phenylpiperazine,
(26) 1-ethyl-4-(3-phenyl-4-methoxy-5-chloromethyl)-phenylpiperazine,
(27) 1-ethyl-4-{3-phenyl-4-methoxy-5-[1-fluoro-(4-pentenyl)]}phenylpiperazine,
(28) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-fluorobutyl)]phenylpiperazine,
(29) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-fluoropentyl)]phenylpiperazine,
(30) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine,
(31) 1-ethyl-4-[3-(2-tolyl)-4-fluoro-5-(1-fluorobutyl)]phenylpiperazine,
(32) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoro-3-methylbutyl)]phenylpiperazine,
(33) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(l-fluoroethyl)]phenylpiperazine,
(34) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine,
(35) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine,
(36) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1,1-difluoropropyl)]phenylpiperazine,
(37) 1-ethyl-4-(3,5-diphenyl-4-methoxy)phenylpiperazine,
(38) 1-ethyl-4-(3-phenyl-4-methoxy)phenylpiperazine,
(39) 1-ethyl-4-(3.5-diphenyl-4-hydroxy)phenylpiperazine,
(40) 1-ethyl-4-(3-phenyl-4-methoxy-5-propyl)phenylpiperazine,
(41) 1-ethyl-4-(3,5-diphenyl-4-isopropoxy)phenylpiperazine,
(42) 1-ethyl-4-(3-phenyl-4-isopropoxy)phenylpiperazine,
(43) 1-ethyl-4-(3-phenyl-4-hydroxy)phenylpiperazine,
(44) 1-ethyl-4-[2-methoxy-3-phenyl-5-(3-hydroxypropyl)]phenylpiperazine,
(45) 1-hydroxyethyl-4-(3,5-diphenyl-4-methoxy)phenylpiperazine,

(46) 1-ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-propyl)]phenylpiperazine,
(47) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxyethyl)]phenylpiperazine,
(48) 1-ethyl-4-[2-methoxy-3-phenyl-5-(2-hydroxyethyl)]phenylpiperazine,
(49) 1-ethyl-4-[3-phenyl-4-methoxy-5-(3-methoxypropyl)]phenylpiperazine,
(50) 1-ethyl-4-[3-phenyl-4-methoxy-5-(3-methoxymethoxypropyl)]phenylpiperazine,
(51) 1-ethyl-4-(3-phenyl-4-methoxy-5-ethyl)phenylpiperazine,
(52) 1-ethyl-4-[3-phenyl-4-methoxy-5-(3-cyanopropyl)]phenylpiperazine,
(53) 1-(2-fluoroethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-propyl]phenylpiperazine,
(54) l-ethyl-4-[3-(4-methoxyphenyl)-4-methoxy-5-propyl]phenylpiperazine,
(55) 1-ethyl-4-(3-phenyl-4-methoxy-5-methoxycarbonyl)phenylpiperazine,
(56) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxypropyl)]phenylpiperazine,
(57) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-fluoroethyl)]phenylpiperazine,
(58) 1-ethyl-4-[3-phenyl-4-methoxy-5-(3-fluoropropyl)]phenylpiperazine,
(59) 1-ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-isopropyl]phenylpiperazine,
(60) 1-ethyl-4-[3-(4-fluorophenyl)-4-methoxy-6-isopropyl]phenylpiperazine,
(61) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxyisopropyl)]phenylpiperazine,
(62) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-butoxypropyl)]phenylpiperazine,
(63) 1-ethyl-4-(3-phenyl-4-methoxy-5-propionyl)-phenylpiperazine,
(64) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxypropyl)]phenylpiperazine,
(65) 1-ethyl-4-[3-(2-fluorophenyl)-4-methoxy-5-propyl]phenylpiperazine,
(66) 1-ethyl-4-[3-(4-trifluoromethylphenyl)-4-methoxy-5-propyl]phenylpiperazine,
(67) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-fluoroisopropyl)]phenylpiperazine,
(68) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxyisopropyl)]phenylpiperazine,
(69) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-fluoropropyl)]phenylpiperazine,
(70) 1-ethyl-4-(3-phenyl-4-methoxy-5-cyano)phenylpiperazine,
(71) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-furanyl)]-phenylpiperazine,
(72) 1-ethyl-4-[3-(2,4-difluorophenyl)-4-methoxy-5-propyl]phenylpiperazine,
(73) 1-ethyl-4-(3-phenyl-4-methoxy-5-phenylacetyl)-phenylpiperazine,
(74) 1-ethyl-4-[3-phenyl-4-methoxy-5-(4-fluorophenyl)acetyl]phenylpiperazine,
(75) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxyphenethyl)]phenylpiperazine,
(76) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-tetrahydrofuranyl)]phenylpiperazine,
(77) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-fluorophenethyl)]phenylpiperazine,
(78) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridyl)]-phenylpiperazine,
(79) 1-ethyl-4-{3-phenyl-4-methoxy-5-[4-fluoro-(1-hydroxyimino)phenethyl]}phenylpiperazine,
(80) 1-ethyl-4-{3-phenyl-4-methoxy-5-[1-fluoro-2-(2-pyridyl)ethyl]}phenylpiperazine,
(81) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-propenyl)]-phenylpiperazine,
(82) 1-ethyl-4-[3-(3-fluorophenyl)-4-methoxy-5-propyl]phenylpiperazine,
(83) 1-ethyl-4-(3-phenyl-4-methoxy-5-hydroxymethyl)-phenylpiperazine,
(84) 1-ethyl-4-[3-phenyl-4-methoxy-5-(4-pyridyl)-acetyl]phenylpiperazine,
(85) 1-ethyl-4-(3-phenyl-4-methoxy-5-methanesulfinyl)phenylpiperazine,
(86) 1-ethyl-4-(3-phenyl-4-methoxy-5-ethanesulfinyl)phenylpiperazine,
(87) 1-ethyl-4-(3-phenyl-4-methoxy-5-formyl)-phenylpiperazine,
(88) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1,3-dioxan-2-yl)]phenylpiperazine,
(89) 1-ethyl-4-(3-phenyl-4-methoxy-5-cyclopropaneacetyl)phenylpiperazine,
(90) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridylcarbonyl)]phenylpiperazine,
(91) 1-ethyl-4-(3-phenyl-4-methoxy-5-amino)phenylpiperazine,
(92) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-ethoxycarbonylethyl)]phenylpiperazine,
(93) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridyl)-hydroxymethyl]phenylpiperazine,
(94) 1-ethyl-4-(3-phenyl-5-propyl-6-methoxy)phenylpiperazine,
(95) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-acetylethyl)]phenylpiperazine,
(96) 1-ethyl-4-{3-phenyl-4-methoxy-5-[1-(2-pyridylmethoxy)propyl]}phenylpiperazine,
(97) 1-ethyl-4-[3-(2-tolyl)-4-methoxy-5-propyl]-phenylpiperazine,
(98) 1-ethyl-4-(3-phenyl-4-methoxy-5-propylamino)-phenylpiperazine,
(99) 1-(3-phenyl-4-hydroxy-5-phenylacetyl)phenylpiperazine,
(100) 1-ethyl-4-(3-phenyl-4-methoxy-5-benzylsulfinyl)phenylpiperazine,
(101) 1-ethyl-4-(3-phenyl-4-methoxy-5-benzenesulfonylamino)phenylpiperazine,
(102) 1-ethyl-4-{3-phenyl-4-methoxy-5-[1-fluoro-2-(4-pyridyl)ethyl]}phenylpiperazine,
(103) 1-ethyl-4-[3-phenyl-4-methoxy-5-(N-ethanesulfonyl-N-methylamino)]phenylpiperazine,

(104) 1-ethyl-4-(3-phenyl-4-methoxy-5-ethylaminosulfonyl)phenylpiperazine,
(105) 1-ethyl-4-(3-phenyl-4-methoxy-5-aminosulfonyl)phenylpiperazine,
(106) 1-(3-phenyl-4-methoxy-5-phenylacetyl)-phenylpiperazine,
(107) 1-benzyl-4-(3-phenyl-4-methoxy-5-phenylacetyl)phenylpiperazine,
(108) 1-ethyl-4-[3-phenyl-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(109) 1-hydroxyethyl-4-(3-phenyl-4-methoxy-5-phenylacetyl)phenylpiperazine,
(110) 1-ethyl-4-[3-phenyl-5-(1-fluoropropyl)]-phenylpiperazine,
(111) 1-ethyl-4-(3-phenyl-5-propionyl)phenylpiperazine,
(112) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(113) 1-ethyl-4-[3-(2-methoxyphenyl)-4-methoxy-5-propyl]phenylpiperazine,
(114) 1-ethyl-4-(3-phenyl-4-methoxy-5-ethanesulfonyl)phenylpiperazine,
(115) 1-ethyl-4-(3-phenyl-4-methoxy-5-dimethylaminosulfonyl)phenylpiperazine,
(116) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1-pyrrolidinylsulfonyl)]phenylpiperazine,
(117) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(2,2,2-trifluoroethyl)sulfonylamino]phenylpiperazine,
(118) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(4-fluorophenylsulfonylamino)]phenylpiperazine,
(119) 1-ethyl-4-[3-phenyl-4-chloro-5-(1-hydroxypropyl)]phenylpiperazine,
(120) 1-ethyl-4-(3-phenyl-4-chloro-5-ethanesulfonyl)phenylpiperazine,
(121) 1-ethyl-4-(3-phenyl-4-chloro-5-propionyl)-phenylpiperazine,
(122) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-pyrrolidylsulfonyl)]phenylpiperazine,
(123) 1-ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-(1-fluoropropyl)}phenylpiperazine,
(124) 1-ethyl-4-[3-(2-methoxyphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(125) 1-ethyl-4-[3-(2,4-difluorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(126) 1-ethyl-4-[3-(2-methoxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(127) 1-ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-cyclopropaneaminosulfonyl}phenylpiperazine,
(128) 1-ethyl-4-[3-phenyl-4-chloro-5-(1-methylpropyl)]phenylpiperazine,
(129) 1-ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-cyclopropylmethylsulfonyl}phenylpiperazine,
(130) 1-ethyl-4-(3-phenyl-4-fluoro-5-ethanesulfonyl)phenylpiperazine,
(131) 1-[3-(4-pyridyl)propyl]-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(132) 1-propyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(133) 1-ethyl-4-[3-(2-hydroxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(134) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(135) l-ethyl-4-[3-(2-tolyl)-4-chloro-5-dimethylaminosulfonyl]phenylpiperazine,
(136) 1-ethyl-4-[3-(2-tolyl)-4-fluoro-5-methanesulfonyl]phenylpiperazine,
(137) 1-ethyl-4-[3-(2-chloro-4-fluorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(138) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-ethylpropyl)]phenylpiperazine,
(139) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-methanesulfonyl]phenylpiperazine,
(140) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonyl]phenylpiperazine,
(141) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoro-4-pentenyl)]phenylpiperazine,
(142) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propylaminosulfonyl]phenylpiperazine,
(143) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-ethanesulfonylamino]phenylpiperazine,
(144) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(2,2,2-trifluoroethyl)sulfonylamino]phenylpiperazine,
(145) 1-ethyl-4-[3-(2-tolyl)-4-cyano-5-(1-fluoropropyl)]phenylpiperazine,
(146) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(3-chloropropyl)sulfonylamino]phenylpiperazine,
(147) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-phenylaminosulfonyl]phenylpiperazine,
(148) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-benzyloxymethyl]phenylpiperazine,
(149) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propoxymethyl]phenylpiperazine,
(150) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(4-pyridyl)-methoxymethyl]phenylpiperazine,
(151) 1-ethyl-4-(3-phenyl-4-methoxy-5-propanesulfonyl)phenylpiperazine,
(152) 1-ethyl-4-(3-phenyl-4-methoxy-5-butanesulfonyl)phenylpiperazine,
(153) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-fluoroethane)sulfonyl]phenylpiperazine,
(154) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-ethoxymethyl]phenylpiperazine,
(155) 1-methyl-4-[3-(2-tolyl)-4-chloro-5-(1-hydroxybutyl)]phenylpiperazine,
(156) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-allyloxymethyl]phenylpiperazine.
(157) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-cyclopropylmethoxymethyl]phenylpiperazine,
(158) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-pyrrolidinyl)]phenylpiperazine,
(159) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazine,
(160) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-benzylsulfonylamino]phenylpiperazine,
(161) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-propanesulfonyl]phenylpiperazine,

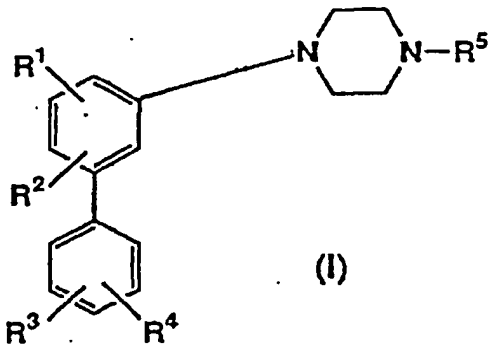
(162) 1-ethyl-4-{3-phenyl-4-methoxy-5-[3-(4-fluorophenoxy)propane]sulfonyl}phenylpiperazine,
(163) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-isopropylsulfonylamino]phenylpiperazine,
(164) 1-ethyl-4-[3-phenyl-4-methoxy-5-(2-cyanoethylsulfonyl)]phenylpiperazine,
(165) 1-ethyl-4-(3-phenyl-4-chloro-5-propanesulfonylamino)phenylpiperazine,
(166) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-difluoromethyl]phenylpiperazine.
(167) 1-ethyl-4-[3-phenyl-4-methoxy-5-(1,1-difluoropropyl)]phenylpiperazine,
(168) 1-ethyl-4-[3-(4-methoxyphenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(169) 1-methyl-4-[3-(2-chlorophenyl)-4-chloro-5-methanesulfonylamino]phenylpiperazine,
(170) 1-ethyl-4-[3-(2,4-dichlorophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(171) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-(1,3-dithian-2-yl)]phenylpiperazine,
(172) 1-ethyl-4-[3-phenyl-4-chloro-5-propanesulfonyl]phenylpiperazine,
(173) 1-ethyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylaminomethyl]phenylpiperazine,
(174) 1-methyl-4-[3-(4-fluorophenyl)-4-methoxy-5-propanesulfonyl]phenylpiperazine,
(175) 1-ethyl-4-[3-(2-ethylphenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(176) 1-hydroxyethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(177) 1-ethyl-4-[3-(2-formylphenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(178) 1-ethyl-4-[3-(2-cyanophenyl)-4-chloro-5-propanesulfonylamino]phenylpiperazine,
(179) 1-(2-pyridylethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(180) 1-(2-pyridylmethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(181) 1-(3-pyridylmethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(182) 1-(4-pyridylethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(183) 1-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(184) 1-(2-fluoroethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethanesulfonyl]phenylpiperazine,
(185) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-propenyl)]phenylpiperazine,
(186) 1-ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-chloropropyl)]phenylpiperazine,
(187) 1-methyl-4-[3-phenyl-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(188) 1-methyl-4-[3-(2-hydroxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(189) 1-ethyl-4-[3-(2-fluoromethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(190) 1-methyl-4-{3-(2-fluoromethylphenyl)-4-chloro-5-[1-fluoropropyl]}phenylpiperazine,
(191) 1-ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-[1-fluoropropyl]}phenylpiperazine,
(192) 1-[2-(2-pyridyl)ethyl]-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(193) 1-[2-(2-pyridyl)ethyl]-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(194) 1-ethyl-4-[3-(2,6-xylyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(195) 1-ethyl-4-{3-(2-trifluoromethylphenyl)-4-chloro-5-[1-fluoropropyl]}phenylpiperazine,
(196) 1-ethyl-4-[3-(2-ethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(197) 1-(2-hydroxyethyl)-4-[3-(2-ethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazine,
(198) 1-(2-hydroxyethyl)-4-{3-(2-trifluoromethylphenyl)-4-chloro-5-[1-fluoropropyl]}phenylpiperazine,
(199) 1-methyl-4-{3-(2-tolyl)-4-chloro-5-[1-fluoropropyl]}phenylpiperazine, and
(200) 1-(2-hydroxyethyl)-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-[1-fluoropropyl]}phenylpiperazine.

6. A therapeutic and ameliorative agent for a mental disorder, which comprises a biphenyl derivative or a pharmacologically acceptable salt thereof as set forth in Claim 1 as an active ingredient.

7. A therapeutic and ameliorative agent for a mental disorder as set forth in Claim 6, wherein the mental disorder is at least one selected from the group consisting of cerebrovascular disorder, aggressive behavior due to senile dementia, mental excitation, poriomania, delirium, hallucination, hyperkinesia, schizophrenia, emotional disturbance, depression, neurosis, psychophysiologic disorder and anxiety neurosis.

8. A therapeutic and ameliorative agent for diseases against which dopamine 2 receptor antagonism and/or serotonin 2 receptor antagonism is efficacious, comprising a biphenyl derivative or a pharmacologically acceptable salt thereof as set forth in Claim 1 as an active ingredient.

9. A process for the preparation of a biphenyl derivative represented by the following formula (I) :



(I)

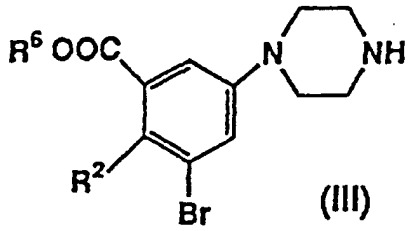
wherein R^1 represents a halogenated C_1-C_6 alkyl group;

R^2 represents a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a C_1-C_6 alkoxyalkyl group, a C_1-C_6 alkoxy group or a halogenated C_1-C_6 alkoxy group;

R^3 represents a cyano group;

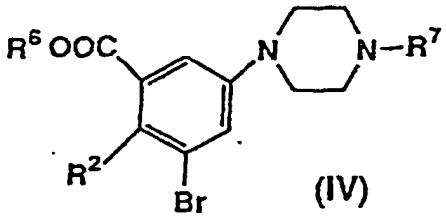
R^4 represents a hydrogen atom, a halogen atom, a C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, a hydroxyiminomethyl group or a formyl group; and

R^5 represents a hydroxy C_1-C_6 alkyl group; which comprises protecting a phenylpiperazine derivative represented by the following formula (III):



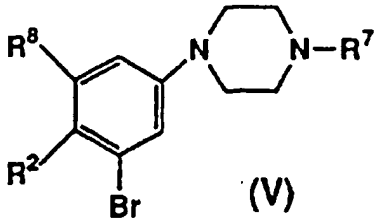
(III)

wherein R^2 is as defined above; and R^6 represents a C_1-C_6 alkyl group,
to form a protected phenylpiperazine derivative represented by the following formula (IV):



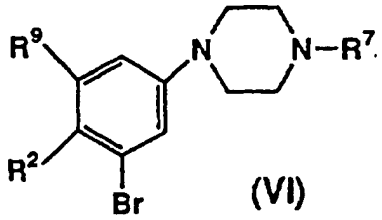
(IV)

wherein R^2 and R^6 are each as defined above; and R^7 represents an amino-protecting group,
reacting the derivative (IV) with an alkylmagnesium halide to form a protected hydroxyalkylphenylpiperazine derivative represented by the following formula (V):



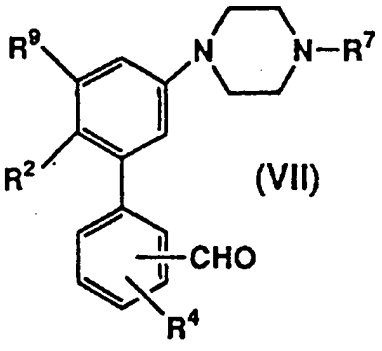
(V)

wherein R^2 and R^7 are each as defined above; and R^8 represents a hydroxyalkyl group,
reacting the derivative (V) with a halogenating agent to form a protected halogenated alkylphenylpiperazine derivative represented by the following formula (VI):



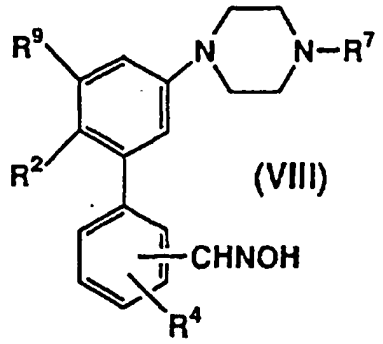
(VI)

wherein R^2 and R^7 are each as defined above; and R^9 represents a halogenated alkyl group,
reacting the derivative (VI) with 2-(1,3,2-dioxaborinan-2-yl)benzaldehyde in the presence of tetrakis(triphenylphosphine)palladium (0) and cesium carbonate to form a protected halogenated alkylbiphenylpiperazine derivative represented by the following formula (VII):



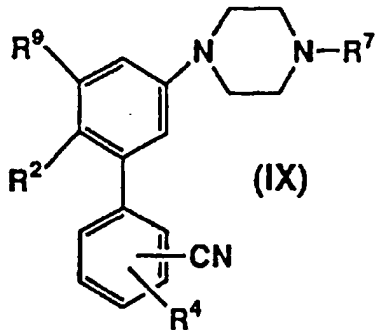
(VII)

wherein R^2, R^4, R^7 and R^9 are each as defined above,
reacting the derivative (VII) with hydroxylamine to form a protected halogenated alkyl oxime biphenylpiperazine derivative represented by the following formula (VIII):



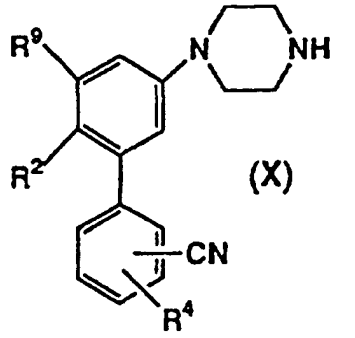
(VIII)

wherein R^2, R^4, R^7 and R^9 are each as defined above,
reacting the derivative (VIII) with acetic anhydride in the presence of pyridine and 4-dimethylaminopyridine to form a protected halogenated alkylcyanobiphenylpiperazine derivative represented by the following formula (IX):



(IX)

wherein R^2, R^4, R^7 and R^9 are each as defined above,
treating the derivative (IX) with an acid to form a halogenated alkylcyanobiphenylpiperazine derivative represented by the following formula (X):

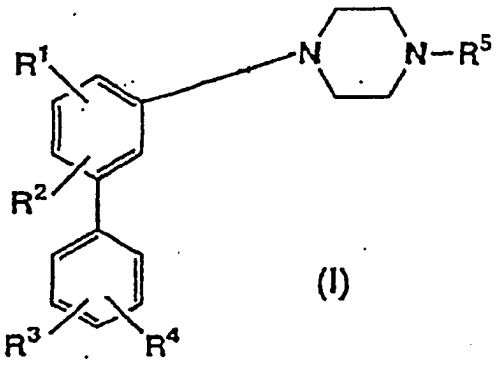


(X)

wherein R^2, R^4 and R^9 are each as defined above,
and reacting the derivative (X) with a halogenated alkanol.

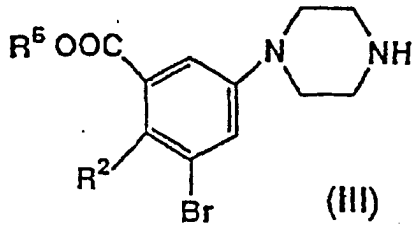
10. The process as set forth in Claim 9, wherein the halogenating agent is diethylaminosulfur trifluoride.

11. A process for the preparation of a biphenyl derivative represented by the following formula (I):



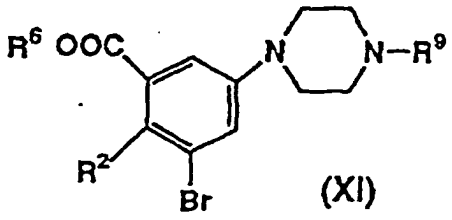
(I)

wherein R^1 represents a C_1-C_6 alkylsulfonylamino group;
R^2 represents a halogen atom;
R^3 and R^4 may be the same or different from each other and each represents a C_1-C_6 alkyl group;
R^5 represents a hydrogen atom, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, a heteroarylalkyl group, an aralkyl group, a C_1-C_6 alkoxycarbonyl group or an aryloxycarbonyl group;
which comprises reacting a phenylpiperazine derivative represented by the following formula (III):



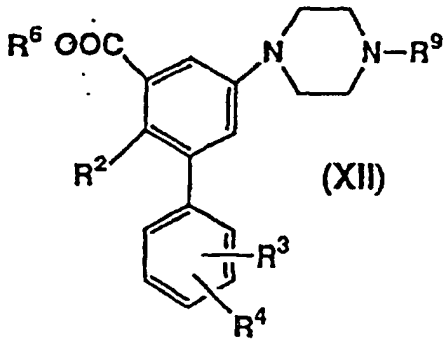
(III)

wherein R^2 is as defined above; and R^6 represents a C_1-C_6 alkyl group,
with an alkyl halide to form a phenylalkylpiperazine derivative represented by the following formula (XI):



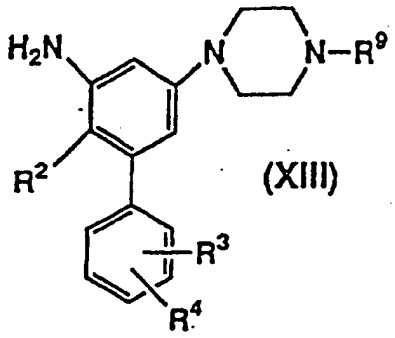
(XI)

wherein R^2 and R^6 are each as defined above and R^9 represents a halogenated alkyl group,
reacting the derivative (XI) with tolylboric acid in the presence of palladium acetate to form a biphenylalkylpiperazine derivative represented by the following formula (XII):



(XII)

wherein R^2, R^3, R^4, R^6 and R^9 are each as defined above, hydrolyzing the derivative (XII), reacting the product of the hydrolysis with ethyl chlorocarbonate in the presence of a base, reacting the product of this reaction with sodium azide and a base successively to form an aminobiphenylalkylpiperazine derivative represented by the following formula (XIII):

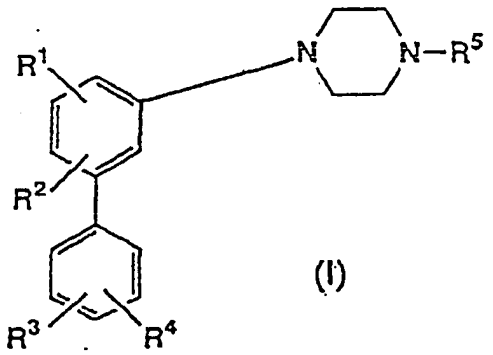


(XIII)

wherein R^2, R^3, R^4 and R^9 are each as defined above,
and reacting the derivative (XIII) with an alkylsulfonyl halide;
wherein the term heteroaryl group denotes a thienyl group, furanyl group, pyranyl group, imadazolyl group, thiazolyl group, pyridyl group or pyrazyl group; the term heteroarylalkyl group denotes a thienylmethyl group, furfuryl group, imidazolylmethyl group, thiazolylmethyl group, pyridylmethyl group or pyrazylmethyl group; and the term halogenated heteroarylalkyl group denotes a heteroarylalkyl group as defined above in which at least one hydrogen atom is replaced by a halogen atom; and wherein the term aryl group denotes an unsubstituted aryl group, a tolyl group, a xylyl group, a methoxyphenyl group, a chlorophenyl group, a bromophenyl group, a flourophenyl group, a nitrophenyl group or a cyanophenyl group.

12. The process as set forth in Claim 11, wherein the base used in the reaction of the product of the hydrolysis with ethyl chlorocarbonate is triethylamine.

13. A process for the preparation of a biphenyl derivative represented by the following formula (I):



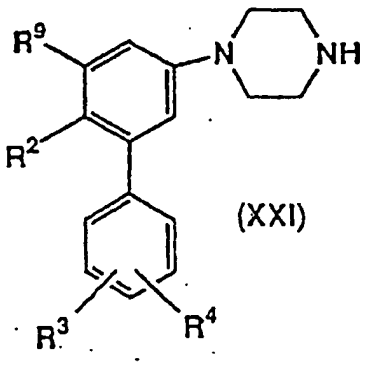
(I)

wherein R^1 represents a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a cyano group, a pyrrolidyl group, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a cyano C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, an amino C_1-C_6 alkyl group, a cycloalkyl group, a cycloalkylalkyl group, a C_1-C_6 alkoxyalkyl group, a heteroarylalkyl group, a halogenated heteroarylalkyl group, a C_1-C_6 acylalkyl group, a heteroarylalkoxyalkyl group, a cycloalkyloxyalkyl group, an aralkyloxyalkyl group, an alkenyloxyalkyl group, a C_1-C_6 alkoxycarbonylalkyl group, a C_1-C_6 alkoxyalkoxyalkyl group, an arylhydroxyalkyl group, a hydroxyheteroarylalkyl group, a cycloalkylalkoxyalkyl group, an alkenyl group, a halogenated alkenyl group, an alkynyl group, an aralkyl group, a halogenated aralkyl group, a hydroxyaralkyl group, a halogenated hydroxyiminoaralkyl group, a C_1-C_6 alkoxy group, a halogenated C_1-C_6 alkoxy group, a C_1-C_6 alkoxyalkoxy group, an aryl group, a hydroxyaryl group, a halogenated aryl group, a C_1-C_6 alkoxyaryl group, a heteroaryl group, a hydroxyheteroaryl group, a halogenated heteroaryl group, a C_1-C_6 alkoxyheteroaryl group, a formyl group, a C_1 - C_6 acyl group, an aromatic acyl group, a heteroaromatic acyl group, an aralkylcarbonyl group, a cycloalkylalkylcarbonyl group, a heteroarylalkylcarbonyl group, a halogenated aralkylcarbonyl group, a C_1-C_6 alkoxycarbonyl group, an aryloxycarbonyl group, a C_1-C_6 alkylamino group, a C_1-C_6 alkylsulfonylamino group, a halogenated C_1-C_6 alkylsulfonylamino group, an arylsulfonylamino group, a halogenated arylsulfonylamino group, an aralkylsulfonyl amino group, a cycloether group, a C_1-C_6 cyclic acetal group, a C_1-C_6 cyclic thioacetal group, a C_1-C_6 alkylsulfinyl group, an arylsulfinyl group, an aralkylsulfinyl group, a heteroarylsulfinyl group, a C_1-C_6 alkylsulfonyl group, an arylsulfonyl group, an aralkylsulfonyl group, a heteroarylsulfonyl group, a cycloalkylsulfonyl group, an aminosulfonyl group, a C_1-C_6 alkylaminosulfonyl group, an arylaminosulfonyl group, a pyrrolidylsulfonyl group, a cycloalkylaminosulfonyl group, a halogenated C_1-C_6 alkylsulfonyl group, a halogenated aryloxy C_1-C_6 alkylsulfonyl group or a cyano C_1-C_6 alkylsulfonyl group;

R^2 and R^3 may be the same or different from each other and each represents a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a C_1-C_6 alkoxyalkyl group, a C_1-C_6 alkoxy group or a halogenated C_1-C_6 alkoxy group;

R^4 represents a hydrogen atom, a halogen atom, a C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, a hydroxyiminomethyl group or a formyl group;

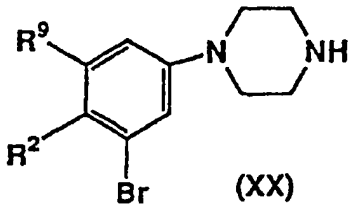
R^5 represents a hydrogen atom, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, a heteroarylalkyl group, an aralkyl group, a C_1-C_6 alkoxycarbonyl group or an aryloxycarbonyl group;
which comprises, reacting a biphenylpiperazine derivative represented by the following formula (XXI):



(XXI)

wherein R^2, R^3 and R^4 are each as defined above and R^9 represents a halogenated alkyl group, with an active derivative represented by the formula: R^5L (wherein R^5 is as defined above; and L represents a leaving group);
wherein the term heteroaryl group denotes a thienyl group, furanyl group, pyranyl group, imadazolyl group, thiazolyl group, pyridyl group or pyrazyl group; the term heteroarylalkyl group denotes a thienylmethyl group, furfuryl group, imidazolylmethyl group, thiazolylmethyl group, pyridylmethyl group or pyrazylmethyl group; and the term halogenated heteroarylalkyl group denotes a heteroarylalkyl group as defined above in which at least one hydrogen atom is replaced by a halogen atom; and wherein the term aryl group denotes an unsubstituted aryl group, a tolyl group, a xylyl group, a methoxyphenyl group, a chlorophenyl group, a bromophenyl group, a flourophenyl group, a nitrophenyl group or a cyanophenyl group.

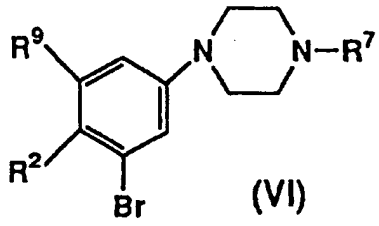
14. The process as set forth in Claim 13, which further comprises reacting a halogenated alkylphenylpiperazine derivative represented by the following formula (XX):



(XX)

wherein R^2 is as defined above and R^9 represents a halogenated alkyl group, with a 2-(1,3,2-dioxaborinan-2-yl)benzene derivative or a phenylboric acid derivative in the presence of triphenylphosphinepalladium and tripotassium phosphate to form a biphenylpiperazine derivative represented by the above formula (XXI).

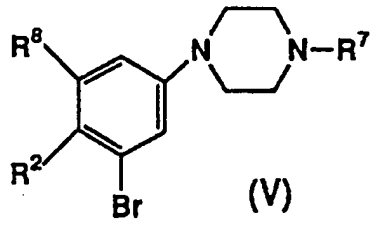
15. The process as set forth in Claim 14, which further comprises deprotecting a protected halogenated alkylphenylpiperazine derivative represented by the following formula (VI):



(VI)

wherein R^2 and R^9 are each as defined above; and R^7 represents an amino-protecting group, to form a halogenated alkylphenylpiperazine derivative represented by the above formula (XX).

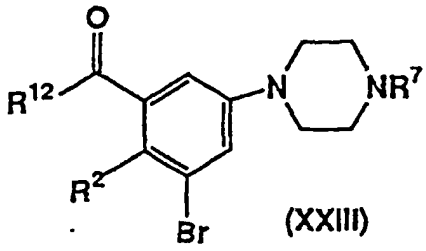
16. The process as set forth in Claim 15, which further comprises reacting a protected hydroxyalkylphenylpiperazine derivative represented by the following formula (V):



(V)

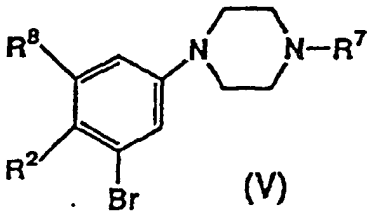
wherein R^2 and R^7 are each as defined above; and R^8 represents a hydroxyalkyl group,
with a halogenating agent to form a protected halogenated alkylphenylpiperazine derivative represented by the above formula (VI).

17. The process as set forth in Claim 15, which further comprises reducing a protected acylphenylpiperazine derivative represented by the following formula (XXIII):



(XXIII)

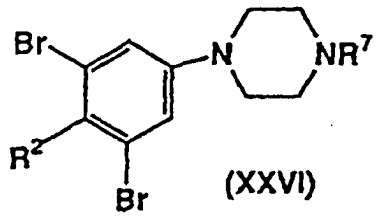
wherein R^2 and R^7 are each as defined above; and R^{12} represents a C_1-C_6 alkyl group,
into a protected hydroxyalkylphenylpiperazine derivative represented by the following formula (V):



(V)

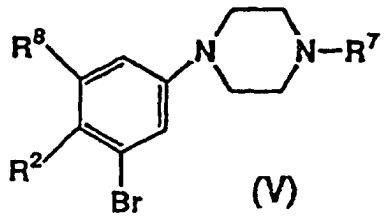
wherein R^2 and R^7 are each as defined above; and R^8 represents a hydroxyalkyl group,
and reacting the derivative (V) with a halogenating agent to form a protected halogenated alkylphenylpiperazine derivative represented by the above formula (VI).

18. The process as set forth in Claim 15, which further comprises reacting a protected dibromophenylpiperazine derivative represented by the following formula (XXVI):



(XXVI)

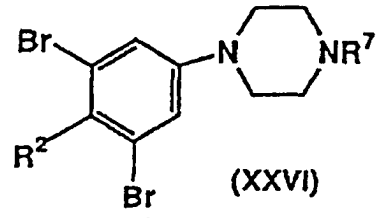
wherein R^2 and R^7 are each as defined above,
with a C_1-C_6 aliphatic aldehyde in the presence of a base to form a protected hydroxyalkylphenylpiperazine derivative represented by the following formula (V):



(V)

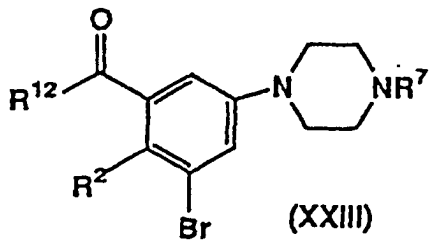
wherein R^2 and R^7 are each as defined above; and R^8 represents a hydroxyalkyl group,
and reacting the derivative (V) with a halogenating agent to form a protected halogenated alkylphenylpiperazine derivative represented by the above formula (VI).

19. The process as set forth in Claim 15, which further comprises reacting a protected dibromophenylpiperazine derivative represented by the following formula (XXVI):



(XXVI)

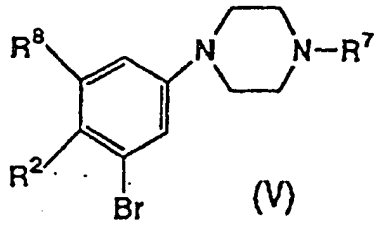
wherein R^2 and R^7 are each as defined above,
with an acid anhydride in the presence of a base to form a protected acylphenylpiperazine derivative represented by the following formula (XXIII):



(XXIII)

wherein R^2 and R^7 are each as defined above; and R^{12} represents a C_1-C_6 alkyl group,

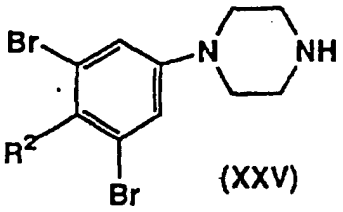
reducing the derivative (XXIII) into a protected hydroxyalkylphenylpiperazine derivative represented by the following formula (V):



(V)

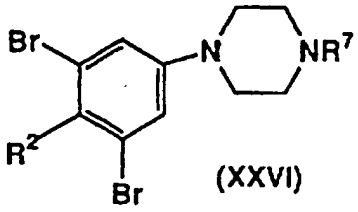
wherein R^2 and R^7 are each as defined above; and R^8 represents a hydroxyalkyl group,
and reacting the derivative (V) with a halogenating agent to form a protected halogenated alkylphenylpiperazine derivative represented by the above formula (VI).

20. The process as set forth in Claim 15, which further comprises protecting a dibromophenylpiperazine derivative represented by the following formula (XXV):



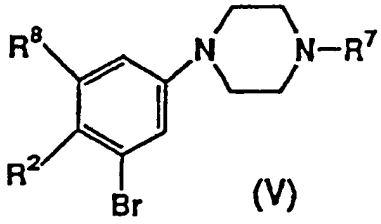
(XXV)

wherein R^2 is as defined above,
to form a protected dibromophenylpiperazine derivative represented by the following formula (XXVI):



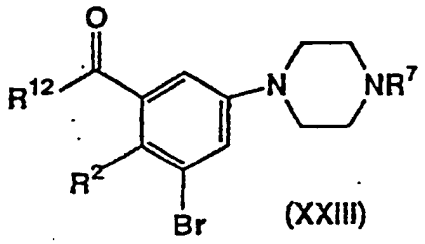
(XXVI)

wherein R^2 and R^7 are each as defined above,
converting the derivative (XXVI) into a protected hydroxyalkylphenylpiperazine derivative represented by the following formula (V):



(V)

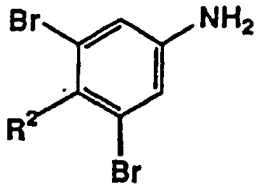
wherein R^2 and R^7 are each as defined above; and R^8 represents a hydroxyalkyl group,
either by reacting the derivative (XXVI) with a C_1-C_6 aliphatic aldehyde in the presence of a base or by reacting the derivative (XXVI) with an acid anhydride in the presence of a base to form a protected acylphenylpiperazine derivative represented by the following formula (XXIII):



(XXIII)

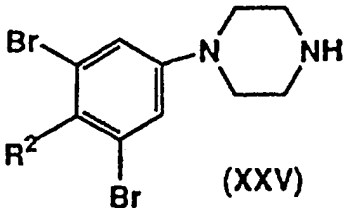
wherein R^2 and R^7 are each as defined above; and R^{12} represents a C_1-C_6 alkyl group,
and reducing the derivative (XXIII), and reacting the derivative (V) with a halogenating agent to form a protected halogenated alkylphenylpiperazine derivative represented by the above formula (VI).

21. The process as set forth in Claim 15, which further comprises reacting a dibromoaniline derivative represented by the following formula (XXIV):



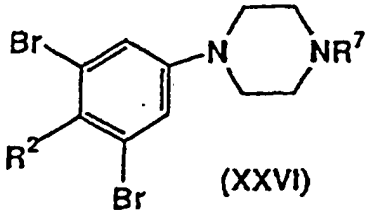
(XXIV)

wherein R^2 is as defined above,
with bis(2-chloroethyl)amine to form a dibromophenylpiperazine derivative represented by the following formula (XXV):



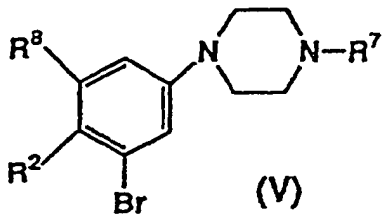
(XXV)

wherein R^2 is as defined above,
protecting the derivative (XXV) to form a protected dibromophenylpiperazine derivative represented by the following formula (XXVI):



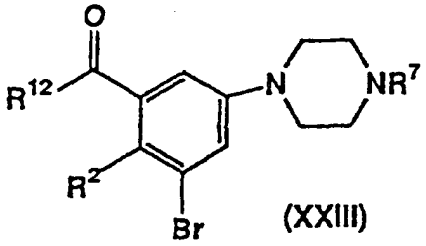
(XXVI)

wherein R^2 and R^7 are each as defined above,
converting the derivative (XXVI) into a protected hydroxyalkylphenylpiperazine derivative represented by the following formula (V):



(V)

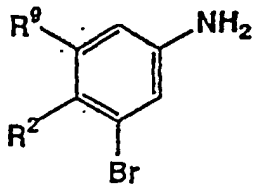
wherein R^2 and R^7 are each as defined above; and R^8 represents a hydroxyalkyl group,
either by reacting the derivative (XXVI) with a C_1-C_6 aliphatic aldehyde in the presence of a base or by reacting the derivative (XXVI) with an acid anhydride in the presence of a base to form a protected acylphenylpiperazine derivative represented by the following formula (XXIII):



(XXIII)

wherein R^2 and R^7 are each as defined above; and R^{12} represents a C_1-C_6 alkyl group,
and reducing the derivative (XXIII), and reacting the derivative (V) with a halogenating agent to form a protected halogenated alkylphenylpiperazine derivative represented by the above formula (VI).

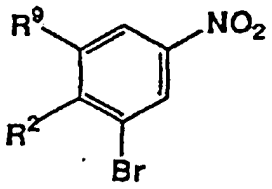
22. The process as set forth in Claim 14, which further comprises reacting a halogenated alkylaniline derivative represented by the following formula (XIX):



(XIX)

wherein R^2 and R^9 are each as defined above,
with bis(2-chloroethyl)amine to form a halogenated alkylphenylpiperazine derivative represented by the above formula (XX).

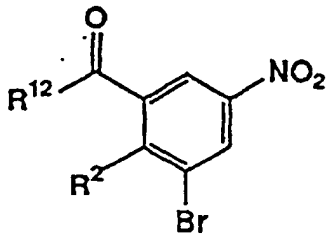
23. The process as set forth in Claim 22, which further comprises reducing a halogenated alkylnitrobenzene derivative represented by the following formula (XVIII):



(XVIII)

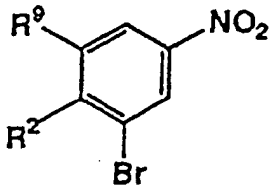
wherein R^2 and R^9 are each as defined above,
into a halogenated alkylaniline derivative represented by the above formula (XIX).

24. The process as set forth in Claim 22, which further comprises reducing an acylnitrobenzene derivative represented by the following formula (XVII):



(XVII)

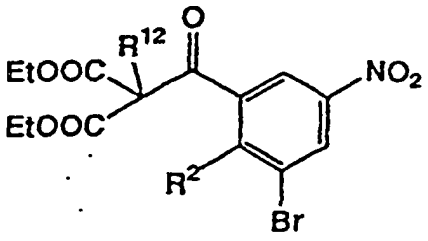
wherein R^2 is as defined above and R^{12} represents a C_1-C_6 alkyl group,
reacting the product of the reduction with a halogenating agent to form a halogenated alkylnitrobenzene derivative represented by the following formula (XVIII):



(XVIII)

wherein R^2 and R^9 are each as defined above,
and reducing the derivative (XVIII) into a halogenated alkylaniline derivative represented by the above formula (XIX).

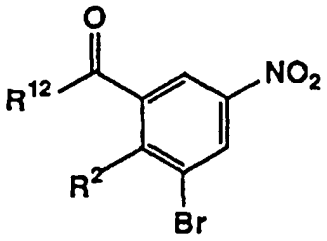
25. The process as set forth in Claim 22, which further comprises reacting a malonic acid ester derivative represented by the following formula (XVI):



(XVI)

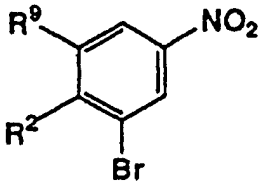
wherein R^2 is as defined above and R^{12} represents a C_1-C_6 alkyl group,

with an acid or a base to form an acylnitrobenzene derivative represented by the following formula (XVII):



(XVII)

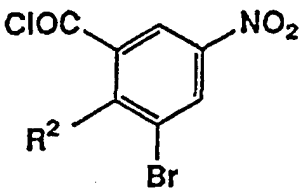
wherein R^2 and R^{12} are each as defined above,
reducing the derivative (XVII), reacting the product of the reduction with a halogenating agent to form a halogenated alkylnitrobenzene derivative represented by the following formula (XVIII):



(XVIII)

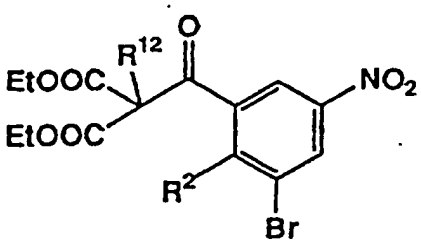
wherein R^2 and R^9 are each as defined above,
and reducing the derivative (XVIII) into a halogenated alkylaniline derivative represented by the above formula (XIX).

26. The process as set forth in Claim 22, which further comprises reacting a nitrobenzoyl chloride derivative represented by the following formula (XV) :



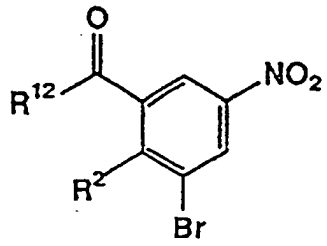
(XV)

wherein R^2 is as defined above,
with an alkylmalonic acid ester in the presence of a base to form a malonic acid ester derivative represented by the following formula (XVI):



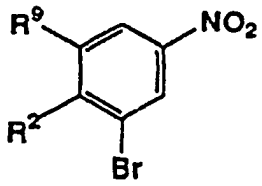
(XVI)

wherein R^2 is as defined above and R^{12} represents a C_1-C_6 alkyl group,
reacting the derivative (XVI) with an acid or. a base to form an acylnitrobenzene derivative represented by the following formula (XVII):



(XVII)

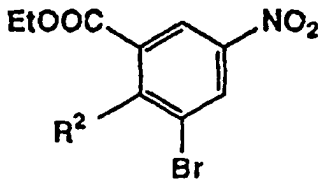
wherein R^2 and R^{12} are each as defined above,
reducing the derivative (XVII), reacting the product of the reduction with a halogenating agent to form a halogenated alkylnitrobenzene derivative represented by the following formula (XVIII):



(XVIII)

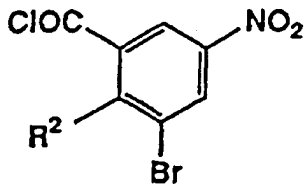
wherein R^2 and R^9 are each as defined above,
and reducing the derivative (XVIII) into a halogenated alkylaniline derivative represented by the above formula (XIX).

27. The process as set forth in Claim 22, which further comprises hydrolyzing a nitrobenzoic acid ester derivative represented by the following formula (XIV):



(XIV)

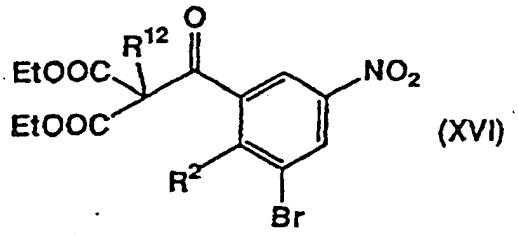
wherein R^2 is as defined above,
reacting the product of the hydrolysis with a chlorinating agent to form a nitrobenzoyl chloride derivative represented by the following formula (XV):



(XV)

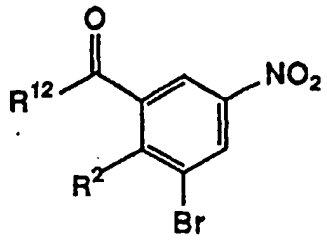
wherein R^2 is as defined above,

reacting the derivative (XV) with an alkylmalonic acid ester in the presence of a base to form a malonic acid ester derivative represented by the following formula (XVI):



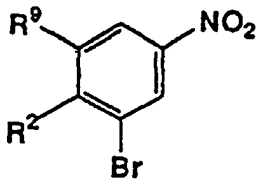
(XVI)

wherein R^2 is as defined above and R^{12} represents a C_1-C_6 alkyl group,
reacting the derivative (XVI) with an acid or a base to form an acylnitrobenzene derivative represented by the following formula (XVII):



(XVII)

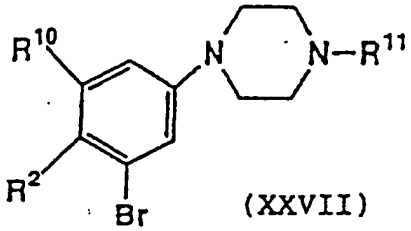
wherein R^2 and R^{12} are each as defined above,
reducing the derivative (XVII), reacting the product of the reduction with a halogenating agent to form a halogenated alkylnitrobenzene derivative represented by the following formula (XVIII) :



(XVIII)

wherein R^2 and R^9 are each as defined above,
and reducing the derivative (XVIII) into a halogenated alkylaniline derivative represented by the above formula (XIX).

28. A phenylpiperazine derivative represented by the following general formula (XXVII) or a salt thereof:



(XXVII)

wherein R^2 represents a hydrogen atom, a halogen atom, a cyano group, a hydroxyl group, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a C_1-C_6 alkoxy group or a halogenated C_1-C_6 alkoxy group; R^{10} represents a halogenated C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, a halogen atom, a C_1-C_6 alkylsulfonyl group, a C_1-C_6 alkoxycarbonyl group, a carboxyl group, an alkenyl group, a (pyridylthio)carbonyl group or a C_1-C_6 acyl group; and R^{11} represents a hydrogen atom, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a hydroxy C_1-C_6 alkyl group, a tri(C_1-C_6 alkyl)silyloxy C_1-C_6 alkyl group, a heteroarylalkyl group, an aralkyl group, a C_1-C_6 alkoxycarbonyl group, an aryloxycarbonyl group or an amino-protecting group;
wherein the term heteroaryl group denotes a thienyl group, furanyl group, pyranyl group, imadazolyl group, thiazolyl group, pyridyl group or pyrazyl group; the term heteroarylalkyl group denotes a thienylmethyl group, furfuryl group, imidazolylmethyl group, thiazolylmethyl group, pyridylmethyl group or pyrazylmethyl group; and the term halogenated heteroarylalkyl group denotes a heteroarylalkyl group as defined above in which at least one hydrogen atom is replaced by a halogen atom; and wherein the term aryl group denotes an unsubstituted aryl group, a tolyl group, a xylyl group, a methoxyphenyl group, a chlorophenyl group, a bromophenyl group, a flourophenyl group, a nitrophenyl group or a cyanophenyl group.

29. The phenylpiperazine derivative or a salt thereof as set forth in Claim 28, wherein R^2 is as defined above; R^{10} represents a halogenated C_1-C_6 alkyl group or a hydroxy C_1-C_6 alkyl group; and R^{11} represents a hydrogen atom, a hydroxy C_1-C_6 alkyl group or an amino-protecting group.

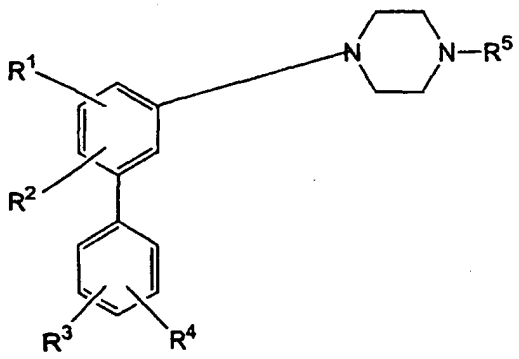
30. The phenylpiperazine derivative or a salt thereof as set forth in Claim 29, wherein R^2 represents a hydrogen atom, a halogen atom, a C_1-C_6 alkyl group, a halogenated C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halognated C_1-C_6 alkoxy group or a cyano group; and R^{10} and R^{11} are each as defined above.

31. A pharmacological composition which comprises a therapeutically or amelioratively effective amount of a biphenyl derivative or a pharmacologically acceptable salt thereof as set forth in Claim 1 and a pharmacologically acceptable vehicle.

32. An use of a biphenyl derivative or a pharmacologically acceptable salt thereof as set forth in Claim 1 for the making of a medicament for treating or ameliorating a disease against which dopamine 2 receptor antagonism and/or serotonin 2 receptor. antagonism is efficacious.

Patentansprüche

1. Biphenylverbindung, dargestellt durch die folgende Formel (I), oder ein pharmakologisch akzeptables Salz davon:



(I)

worin
R^1 ein Wasserstoffatom, ein Halogenatom, eine Hydroxylgruppe, eine Aminogruppe, eine Cyanogruppe, eine Pyrrolidylgruppe, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine Cyano-C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, eine Amino-C_1-C_6-Alkylgruppe, eine Cycloalkylgruppe, eine Cycloalkylalkylgruppe, eine C_1-C_6-Alkoxyalkylgruppe, eine Heteroarylalkylgruppe, eine halogenierte Heteroarylalkylgruppe, eine C_1-C_6-Acylalkylgruppe, eine Heteroarylalkoxyalkylgruppe, eine Cycloalkyloxyalkylgruppe, eine Aralkyloxyalkylgruppe, eine Alkenyloxyalkylgruppe, eine C_1-C_6-Alkoxycarbonylalkylgruppe, eine C_1-C_6-Alkoxyalkoxyalkylgruppe, eine Aryl-

hydroxyalkylgruppe, eine Hydroxyheteroarylalkylgruppe, eine Cycloalkylalkoxyalkylgruppe, eine Alkenylgruppe, eine halogenierte Alkenylgruppe, eine Alkynylgruppe, eine Aralkylgruppe, eine halogenierte Aralkylgruppe, eine Hydroxyaralkylgruppe, eine halogenierte Hydroxyiminoaralkylgruppe, eine C_1-C_6-Alkoxygruppe, eine halogenierte C_1-C_6-Alkoxygruppe, eine C_1-C_6-Alkoxyalkoxygruppe, eine Arylgruppe, eine Hydroxyarylgruppe, eine halogenierte Arylgruppe, eine C_1-C_6-Alkoxyarylgruppe, eine Heteroarylgruppe, eine Hydroxyheteroarylgruppe, eine halogenierte Heteroarylgruppe, eine C_1-C_6-Alkoxyheteroarylgruppe, eine Formylgruppe, eine C_1-C_6-Acylgruppe, eine aromatische Acylgruppe, eine heteroaromatische Acylgruppe, eine Aralkylcarbonylgruppe, eine Cycloalkylalkylcarbonylgruppe, eine Heteroarylalkylcarbonylgruppe, eine halogenierte Aralkylcarbonylgruppe, eine C_1-C_6-Alkoxycarbonylgruppe, eine Aryloxycarbonylgruppe, eine C_1-C_6-Alkylaminogruppe, eine C_1-C_6-Alkylsulfonylaminogruppe, eine halogenierte C_1-C_6-Alkylsulfonylaminogruppe, eine Arylsulfonylaminogruppe, eine halogenierte Arylsulfonylaminogruppe, eine Aralkylsulfonylaminogruppe, eine Cycloethergruppe, eine zyklische C_1-C_6-Acetalgruppe, eine zyklische C_1-C_6-Thioacetalgruppe, eine C_1-C_6-Alkylsulfinylgruppe, eine Arylsulfinylgruppe, eine Aralkylsulfinylgruppe, eine Heteroarylsulfinylgruppe, eine C_1-C_6-Alkylsulfonylgruppe, eine Arylsulfonylgruppe, eine Aralkylsulfonylgruppe, eine Heteroarylsulfonylgruppe, eine Cycloalkylsulfonylgruppe, eine Aminosulfonylgruppe, eine C_1-C_6-Alkylaminosulfonylgruppe, eine Arylaminosulfonylgruppe, eine Pyrrolidylsulfonylgruppe, eine Cycloalkylaminosulfonylgruppe, eine halogenierte C_1-C_6-Alkylsulfonylgruppe, eine halogenierte Aryloxy-C_1-C_6-Alkylsulfonylgruppe oder eine Cyano-C_1-C_6-Alkylsulfonylgruppe repräsentiert;

R^2 und R^3 können dieselben sein oder sich voneinander unterscheiden und jeweils ein Wasserstoffatom, ein Halogenatom, eine Cyanogruppe, eine Hydroxylgruppe, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine C_1-C_6-Alkoxyalkylgruppe, eine C_1-C_6-Alkoxygruppe oder eine halogenierte C_1-C_6-Alkoxygruppe repräsentieren;

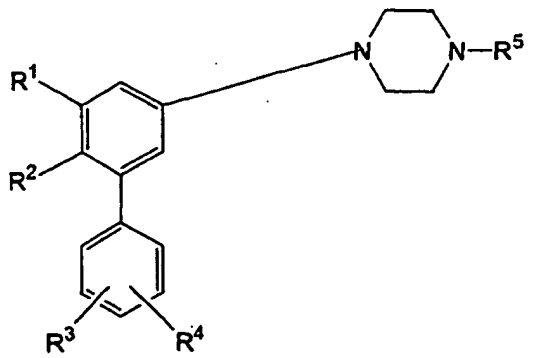
R^4 repräsentiert ein Wasserstoffatom, ein Halogenatom, eine C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, eine Hydroxyiminomethylgruppe oder eine Formylgruppe;

R^5 repräsentiert ein Wasserstoffatom, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, eine Heteroarylalkylgruppe, eine C_1-C_6-Alkoxycarbonylgruppe oder eine Aryloxycarbonylgruppe;

vorausgesetzt, daß die Biphenylverbindung weder 1-[3-Phenyl-4-methyl)-phenyl]-piperazin noch 1-Methyl-4-[(3-phenyl-4-methyl)-phenyl]-piperazin ist, und vorausgesetzt daß R^5 kein Wasserstoffatom repräsentiert, wenn R^1 und R^2 Wasserstoffatome repräsentieren, R^3 ein Wasserstoffatom, ein Halogenatom oder eine Hydroxylgruppe repräsentiert, und wenn R^4 ein Wasserstoff, ein Halogenatom oder eine Formylgruppe repräsentiert;

worin der Begriff Heteroarylgruppe eine Thienylgruppe, Furanylgruppe, Pyranylgruppe, Imidazolylgruppe, Thiazolylgruppe, Pyridylgruppe oder Pyrazylgruppe bezeichnet; der Begriff Heteroarylalkylgruppe eine Thienylmethylgruppe, Furfurylgruppe, Imidazolylmethylgruppe, Thiazolylmethylgruppe, Pyridylmethylgruppe oder Pyrazylmethylgruppe bezeichnet; der Begriff halogenierte Heteroarylalkylgruppe eine wie oben definierte Heteroarylalkylgruppe bezeichnet, bei der zumindest ein Wasserstoffatom durch ein Halogenatom ersetzt ist; und worin der Begriff Arylgruppe eine unsubstituierte Arylgruppe, eine Tolylgruppe, eine Xylylgruppe, eine Methoxyphenylgruppe, eine Chlorophenylgruppe, eine Bromophenylgruppe, eine Fluorophenylgruppe, eine Nitrophenylgruppe oder eine Cyanophenylgruppe bezeichnet.

2. Biphenylverbindung oder deren pharmakologisch akzeptables Salz gemäß Anspruch 1, worin die Biphenylverbindung durch die folgende Formel (II) repräsentiert wird:



(II)

worin R^1, R^2, R^3, R^4 und R^5 jeweils wie oben definiert sind.

3. Biphenylverbindung oder deren pharmakologisch akzeptables Salz gemäß Anspruch 1, worin
R^1 ein Wasserstoffatom, ein Halogenatom, eine Hydroxylgruppe, eine Aminogruppe, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine C_1-C_6-Alkoxygruppe, eine halogenierte C_1-C_6-Alkoxygruppe, eine C_1-C_6-Alkoxyalkylgruppe, eine C_1-C_6-Alkoxyalkoxygruppe, eine Arylgruppe, ein Aralkylgruppe, eine Heteroarylgruppe, eine Heteroarylalkylgruppe, eine halogenierte Heteroarylalkylgruppe, eine Cyano-C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, eine Amino-C_1-C_6-Alkylgruppe, eine C_1-C_6-Alkoxycarbonylgruppe, eine Aryloxycarbonylgruppe, eine Cyanogruppe, eine Formylgruppe, eine C_1-C_6-Acylgruppe, eine Aralkylcarbonylgruppe, eine Cycloethergruppe, eine Alkenylgruppe, eine Alkynylgruppe, eine C_1-C_6-Alkylsulfinylgruppe, eine C_1-C_6-Alkylsulfonylgruppe, eine C_1-C_6-Alkylaminosulfonylgruppe, eine Arylaminosulfonylgruppe, eine C_1-C_6-Alkylsulfonylaminogruppe, eine halogenierte C_1-C_6-Alkylsulfonylaminogruppe oder eine Arylsulfonylaminogruppe repräsentiert;
R^2 und R^3 können dieselben sein oder sich voneinander unterscheiden und jeweils ein Wasserstoffatom, ein Halogenatom, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine C_1-C_6-Alkoxygruppe, eine halogenierte C_1-C_6-Alkoxygruppe oder eine Cyanogruppe repräsentieren;
R^4 repräsentiert ein Wasserstoffatom oder ein Halogenatom;
R^5 repräsentiert ein Wasserstoffatom, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, eine C_1-C_6-Alkoxycarbonylgruppe oder eine Aryloxycarbonylgruppe.

4. Biphenylverbindung oder deren pharmakologisch akzeptables Salz gemäß Anspruch 1, worin R^1 eine halogenierte C_1-C_6-Alkylgruppe oder eine C_1-C_6-Alkylsulfonylaminogruppe ist; R^2 ein Halogenatom oder eine C_1-C_6-Alkoxygruppe ist; R^3 ein Halogenatom, eine C_1-C_6-Alkylgruppe oder eine Cyanogruppe ist; R^4 ein Wasserstoffatom oder ein Halogenatom ist; R^5 ein Wasserstoffatom, eine C_1-C_6-Alkylgruppe oder eine Hydroxy-C_1-C_6-Alkylgruppe ist.

5. Biphenylverbindung oder deren pharmakologisch akzeptables Salz gemäß Anspruch 1, die eine Verbindung ist ausgewählt aus der Gruppe bestehend aus:

(1) 1-[3-(2-Cyanophenyl)-4-chloro-5-(1-fluoropropyl)]-phenylpiperazin,
(2) 1-(2-Hydroxyethyl)-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(3) 1-Ethyl-4- [3-(2-tolyl)-4-chloro-5-ethoxycarbonyl]-phenylpiperazin,
(4) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-amino]phenylpiperazin,
(5) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-propansulfonylamino]phenylpiperazin,
(6) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-ethansulfonylamino]phenylpiperazin,
(7) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-butansulfonylamino]phenylpiperazin,
(8) 1-Methyl-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(9) 1-Ethyl-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(10) 1-Methyl-4-([3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(11) 1-(2-Hydroxyethyl)-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(12) 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(13) 1-Methyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(14) 1(2-Hydroxyethyl)-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(15) 1-Ethyl-4- [3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(16) 1-Methyl-4-[3-(2-tolyl)-4-chloro-5-ethansulfonylamino] phenylpiperazin,
(17) 1-Methyl-4-[3-(2-tolyl)-4-chloro-5-propansulfonylamino]phenylpiperazin,
(18) 1-Methyl-4-[3(-2-tolyl)-4-chloro-5-butansulfonylamino]phenylpiperazin,
(19) 1-Ethyl-4-[3-(2-chlorophenyl)4-chloro-5-ethansulfonylamino]phenylpiperazin,
(20) 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-propansulfonylamino]phenylpiperazin,
(21) 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-butansulfonylamino]phenylpiperazin,
(22) 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-ethansulfonylamino]phenylpiperazin,
(23) 1-Methyl-4- [3-(2-chlorophenyl)-4-chloro-5-propansulfonylamino]phenylpiperazin,
(24) 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-butansulfonylamino]phenylpiperazin,
(25) 1-Ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-ethansulfonylamino]phenylpiperazin,
(26) 1-Ethyl-4- (3-phenyl-4-methoxy-5-chloromethyl)phenylpiperazin,
(27) 1-Ethyl-4-{3-phenyl-4-methoxy-5-[1-fluoro(4-pentenyl)]}phenylpiperazin,
(28) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-fluorobutyl)]-phenylpiperazin,
(29) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-fluoropentyl)]-phenylpiperazin,
(30) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluorobutyl)]-phenylpiperazin,
(31) 1-Ethyl-4-[3-(2-tolyl)-4-fluoro-5-(1-fluorobutyl)]-phenylpiperazin,
(32) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoro-3-methylbutyl)]phenylpiperazin,
(33) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoroethyl)]-phenylpiperazin,

(34) 1-Methyl-4- [3-(2-tolyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazin,
(35) 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazin,
(36) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1,1-difluoropropyl)]phenylpiperazin,
(37) 1-Ethyl-4-(3,5-diphenyl-4-methoxy)phenylpiperazin,
(38) 1-Ethyl-4-(3-phenyl-4-methoxy)phenylpiperazin,
(39) 1-Ethyl-4-(3,5-diphenyl-4-hydroxy)phenylpiperazin,
(40) 1-Ethyl-4-(3-phenyl-4-methoxy-5-propyl)phenylpiperazin,
(41) 1-Ethyl-4-(3,5-diphenyl-4-isopropoxy)phenylpiperazin,
(42) 1-Ethyl-4-(3-phenyl-4-isopropoxy)phenylpiperazin,
(43) 1-Ethyl-4-(3-phenyl-4-hydroxy)phenylpiperazin,
(44) 1-Ethyl-4-[2-methoxy-3-phenyl-5-(3-hydroxypropyl)]-phenylpiperazin,
(45) 1-Hydroxyethyl-4-(3,5-diphenyl-4-methoxy)phenylpiperazin,
(46) 1-Ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-propyl)]-phenylpiperazin,
(47) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxyethyl)]-phenylpiperaz in,
(48) 1-Ethyl-4-[2-methoxy-3-phenyl-5-(2-hydroxyethyl)]-phenylpiperazin,
(49) 1-Ethyl-4- [3-phenyl-4-methoxy-5- (3-methoxypropyl)]-phenylpiperazin,
(50) 1-Ethyl-4- [3-phenyl-4-methoxy-5- (3-methoxymethoxypropyl)]phenylpiperazin,
(51) 1-Ethyl-4-(3-phenyl-4-methoxy-5-ethyl)phenylpiperazin,
(52) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(3-cyanopropyl)]phenylpiperazin,
(53) 1- (2-Fluoroethyl) -4- [3- (4-fluorophenyl)-4-methoxy-5-propyl]phenylpiperazin,
(54) 1-Ethyl-4-[3-(4-methoxyphenyl)-4-methoxy-5-propyl]-phenylpiperazin,
(55) 1-Ethyl-4-(3-phenyl-4-methoxy-5-methoxycarbonyl)-phenylpiperazin,
(56) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxypropyl)]-phenylpiperazin,
(57) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-fluoroethyl)]-phenylpiperazin,
(58) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(3-fluoropropyl)]-phenylpiperazin,
(59) 1-Ethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-isopropyl]phenylpiperazin,
(60) 1-Ethyl-4- [3- (4-fluorophenyl) -4-methoxy-6-isopropyl]phenylpiperazin,
(61) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxyisopropyl)]phenylpiperazin,
(62) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-butoxypropyl)]-phenylpiperazin,
(63) 1-Ethyl-4-(3-phenyl-4-methoxy-5-propionyl)phenylpiperazin,
(64) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxypropyl)]-phenylpiperazin,
(65) 1-Ethyl-4-[3-(2-fluorophenyl)-4-methoxy-5-propyl]-phenylpiperazin,
(66) 1-Ethyl-4- [3-(4-trifluoromethylphenyl)-4-methoxy-5-propyl]phenylpiperazin,
(67) 1-Ethyl-4- [3-phenyl-4-methoxy-5-(1-fluoroisopropyl)]phenylpiperazin,
(68) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-hydroxyisopropyl)]phenylpiperazin,
(69) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-fluoropropyl)]-phenylpiperaz in,
(70) 1-Ethyl-4-(3-phenyl-4-methoxy-5-cyano)phenylpiperazin,
(71) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-furanyl)]phenylpiperazin,
(72) 1-Ethyl-4-[3-(2,4-difluorophenyl)-4-methoxy-5-propyl]phenylpiperazin,
(73) 1-Ethyl-4-(3-phenyl-4-methoxy-5-phenylacetyl)-phenylpiperazin,
(74) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(4-fluorophenyl)-acetyl]phenylpiperazin,
(75) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-hydroxyphenethyl)]phenylpiperazin,
(76) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-tetrahydrofuranyl)]phenylpiperazin,
(77) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-fluorophenethyl)]phenylpiperazin,
(78) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridyl)]phenylpiperazin,
(79) 1-Ethyl-4-{3-phenyl-4-methoxy-5-[4-fluoro-(1-hydroxyimino)phenethyl)}phenylpiperazin,
(80) 1-Ethyl-4-{3-phenyl-4-methoxy-5-[1-fluoro-2-(2-pyridyl)ethyl]}phenylpiperazin,
(81) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-propenyl)]-phenylpiperaz in,
(82) 1-Ethyl-4-[3-(3-fluorophenyl)-4-methoxy-5-propyl]-phenylpiperazin,
(83) 1-Ethyl-4-(3-phenyl-4-methoxy-5-hydroxymethyl)-phenylpiperazin,
(84) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(4-pyridyl)-acetylphenylpiperazin,
(85) 1-Ethyl-4-(3-phenyl-4-methoxy-5-methansulfinyl)-phenylpiperazin,
(86) 1-Ethyl-4-(3-phenyl-4-methoxy-5-ethansulfinyl)-phenylpiperazin,
(87) 1-Ethyl-4-(3-phenyl-4-methoxy-5-formyl)phenylpiperazin,
(88) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1,3-dioxan-2-yl)]phenylpiperazin,
(89) 1-Ethyl-4-(3-phenyl-4-methoxy-5-cyclopropanacetyl)-phenylpiperazin,
(90) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridylcarbonyl)]phenylpiperazin,
(91) 1-Ethyl-4-(3-phenyl-4-methoxy-5-amino)phenylpiperazin,

(92) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-ethoxycarbonylethyl)]phenylpiperazin,
(93) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-pyridyl)hydroxymethyl]phenylpiperazin,
(94) 1-Ethyl-4-(3-phenyl-5-propyl-6-methoxy)phenylpiperazin,
(95) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-acetylethyl)]-phenylpiperazin,
(96) 1-Ethyl-4-{3-phenyl-4-methoxy-5-[1-(2-pyridylmethoxy)propyl]}phenylpiperazin,
(97) 1-Ethyl-4-[3-(2-tolyl)-4-methoxy-5-propyl]phenylpiperazin,
(98) 1-Ethyl-4-(3-phenyl-4-methoxy-5-propylamino)phenylpiperazin,
(99) 1-(3-Phenyl-4-hydroxy-5-phenylacetyl)phenylpiperazin,
(100) 1-Ethyl-4-(3-phenyl-4-methoxy-5-benzylsulfinyl)-phenylpiperazin,
(101) 1-Ethyl-4-(3-phenyl-4-methoxy-5-benzolsulfonylamino)phenylpiperazin,
(102) 1-Ethyl-4-{3-phenyl-4-methoxy-5-[1-fluoro-2-(4-pyridyl)ethyl]}phenylpiperazin,
(103) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(N-ethansulfonyl-N-methylamino)]phenylpiperazin,
(104) 1-Ethyl-4-(3-phenyl-4-methoxy-5-ethylaminosulfonyl)phenylpiperazin,
(105) 1-Ethyl-4-(3-phenyl-4-methoxy-5-aminosulfonyl)-phenylpiperazin,
(106) 1-(3-Phenyl-4-methoxy-5-phenylacetyl)phenylpiperazin,
(107) 1-Benzyl-4-(3-phenyl-4-methoxy-5-phenylacetyl)-phenylpiperazin,
(108) 1-Ethyl-4-[3-phenyl-4-chloro-5-(1-fluoropropyl)]-phenylpiperazin,
(109) 1-Hydroxyethyl-4-(3-phenyl-4-methoxy-5-phenylacetyl)phenylpiperazin,
(110) 1-Ethyl-4-[3-phenyl-5-(1-fluoropropyl)]phenylpiperazin,
(111) 1-Ethyl-4-(3-phenyl-5-propionyl)phenylpiperazin,
(112) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)phenylpiperazin,
(113) 1-Ethyl-4-[3-(2-methoxyphenyl)-4-methoxy-5-propyl]phenylpiperazin,
(114) 1-Ethyl-4-(3-phenyl-4-methoxy-5-ethansulfonyl)-phenylpiperazin,
(115) 1-Ethyl-4-(3-phenyl-4-methoxy-5-dimethylaminosulfonyl)phenylpiperazin,
(116) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1-pyrrolidinylsulfonyl)]phenylpiperazin,
(117) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(2,2,2-trifluoroethyl)sulfonylamino]phenylpiperazin,
(118) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(4-fluorophenylsulfonylamino)]phenylpiperazin,
(119) 1-Ethyl-4-[3-phenyl-4-chloro-5-(1-hydroxypropyl)]-phenylpiperazin,
(120) 1-Ethyl-4-(3-phenyl-4-chloro-5-ethansulfonyl)-phenylpiperazin,
(121) 1-Ethyl-4-(3-phenyl-4-chloro-5-propionyl)phenylpiperazin,
(122) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-pyrrolidylsulfonyl)]phenylpiperazin,
(123) 1-Ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-(1-fluoropropyl)}phenylpiperazin,
(124) 1-Ethyl-4-[3-(2-methoxyphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(125) 1-Ethyl-4-[3-(2,4-difluorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(126) 1-Ethyl-4-[3-(2-methoxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(127) 1-Ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-cyclopropanaminosulfonyl}phenylpiperazin,
(128) 1-Ethyl-4-[3-phenyl-4-chloro-5-(1-methylpropyl)]-phenylpiperazin,
(129) 1-Ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-cyclopropylmethylsulfonyl}phenylpiperazin,
(130) 1-Ethyl-4-(3-phenyl-4-fluoro-5-ethansulfonyl)-phenylpiperazin,
(131) 1- [3- (4-pyridyl)propyl] -4- [3- (2-tolyl) -4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(132) 1-Propyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(133) 1-Ethyl-4-[3-(2-hydroxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(134) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-propansulfonylamino]phenylpiperazin,
(135) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-dimethylaminosulfonyl]phenylpiperazin,
(136) 1-Ethyl-4- [3- (2-tolyl) -4-fluoro-5-methansulfonyl]-phenylpiperazin,
(137) 1-Ethyl-4-[3-(2-chloro-4-fluorophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(138) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-ethylpropyl)]phenylpiperazin,
(139) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-methansulfonyl]-phenylpiperazin,
(140) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-propansulfonyl]-phenylpiperazin,
(141) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoro-4-pentenyl)]phenylpiperazin,
(142) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-propylaminosulfonyl]phenylpiperazin,
(143) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-ethansulfonylamino]phenylpiperazin,
(144) 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(2,2,2-trifluoroethyl)sulfonylamino]phenylpiperazin,
(145) 1-Ethyl-4-[3-(2-tolyl)4-cyano-5-(1-fluoropropyl)]-phenylpiperazin,
(146) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(3-chloropropyl)sulfonylamino]phenylpiperazin,
(147) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-phenylaminosulfonyl]phenylpiperazin,
(148) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-benzyloxymethyl]phenylpiperazin,
(149) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-propoxymethyl]-phenylpiperazin,

(150) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(4-pyridyl)-methoxymethyl]phenylpiperazin,
(151) 1-Ethyl-4-(3-phenyl-4-methoxy-5-propansulfonyl)-phenylpiperaz in,
(152) 1-Ethyl-4-(3-phenyl-4-methoxy-5-butansulfonyl)-phenylpiperazin,
(153) 1-Ethyl-4- [3-phenyl-4-methoxy-5-(2-fluoroethan)-sulfonyl]phenylpiperazin,
(154) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-ethoxymethyl]-phenylpiperazin,
(155) 1-Methyl-4-[3-(2-tolyl)-4-chloro-5-(1-hydroxybutyl)]phenylpiperazin,
(156) 1-Ethyl-4- [3-(2-tolyl)-4-chloro-5-allyloxymethyl]-phenylpiperazin,
(157) 1-Ethyl-4- [3-(2-tolyl)-4-chloro-5-cyclopropylmethoxymethyl]phenylpiperazin,
(158) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1-pyrrolidinyl)]phenylpiperazin,
(159) 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-fluorobutyl)]phenylpiperazin,
(160) 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-benzylsulfonylamino]phenylpiperazin,
(161) 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-propansulfonyl]phenylpiperazin,
(162) 1-Ethyl-4-{3-phenyl-4-methoxy-5-[3-(4-fluorophenoxy)propan]sulfonyl}phenylpiperazin,
(163) 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-isopropylsulfonylamino]phenylpiperazin,
(164) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(2-cyanoethylsulfonyl)]phenylpiperazin,
(165) 1-Ethyl-4-(3-phenyl-4-chloro-5-propansulfonylamino)phenylpiperazin,
(166) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-difluoromethyl]-phenylpiperazin,
(167) 1-Ethyl-4-[3-phenyl-4-methoxy-5-(1,1-difluoropropyl)]phenylpiperazin,
(168) 1-Ethyl-4-[3-(4-methoxyphenyl)-4-chloro-5-propansulfonylamino]phenylpiperazin,
(169) 1-Methyl-4-[3-(2-chlorophenyl)-4-chloro-5-methansulfonylamino]phenylpiperazin,
(170) 1-Ethyl-4-[3-(2,4-dichlorophenyl)-4-chloro-5-propansulfonylamino]phenylpiperazin,
(171) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-(1,3-dithian-2-yl)]phenylpiperazin,
(172) 1-Ethyl-4-[3-phenyl-4-chloro-5-propansulfonyl]-phenylp iperaz in,
(173) 1-Ethyl-4-[3-(2-tolyl)-4-chloro-5-propansulfonylaminomethyl]phenylpiperazin,
(174) 1-Methyl-4-[3-(4-fluorophenyl)-4-methoxy-5-propansulfonyl]phenylpiperazin,
(175) 1-Ethyl-4-[3-(2-ethylphenyl)-4-chloro-5-propansulfonylamino]phenylpiperazin,
(176) 1-Hydroxyethyl-4-[3-(4-fluorophenyl)-4-methoxy-5-ethansulfonyl]phenylpiperazin,
(177) 1-Ethyl-4-[3-(2-formylphenyl)-4-chloro-5-propansulfonylamino]phenylpiperazin,
(178) 1-Ethyl-4-[3-(2-cyanophenyl)-4-chloro-5-propansulfonylamino]phenylpiperazin,
(179) 1-(2-Pyridylethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethansulfonyl]phenylpiperazin,
(180) 1-(2-Pyridylmethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethansulfonyl]phenylpiperazin,
(181) 1-(3-Pyridylmethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethansulfonyl]phenylpiperazin,
(182) 1-(4-Pyridylethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethansulfonyl]phenylpiperazin,
(183) 1- [3-(4-Fluorophenyl)-4-methoxy-5-ethansulfonyl]-phenylpiperazin,
(184) 1-(2-Fluoroethyl)-4-[3-(4-fluorophenyl)-4-methoxy-5-ethansulfonyl]phenylpiperazin,
(185) 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-propenyl)]phenylpiperazin,
(186) 1-Ethyl-4-[3-(2-chlorophenyl)-4-chloro-5-(1-chloropropyl)]phenylpiperazin,
(187) 1-Methyl-4-[3-phenyl-4-chloro-5-(1-fluoropropyl)]-phenylpiperazin,
(188) 1-Methyl-4-[3-(2-hydroxymethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(189) 1-Ethyl-4-[3-(2-fluoromethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(190) 1-Methyl-4-{3-(2-fluoromethylphenyl)-4-chloro-5-[1-fluoropropyl]}phenylpiperazin,
(191) 1-Ethyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-[1-fluoropropyl]}phenylpiperazin,
(192) 1-[2-(2-Pyridyl)ethyl]-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(193) 1-[2-(2-Pyridyl)ethyl]-4-[3-(2-cyanophenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(194) 1-Ethyl-4-[3-(2,6-xylyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(195) 1-Ethyl-4-{3-(2-trifluoromethylphenyl)-4-chloro-5-[1-fluoropropyl]}phenylpiperazin,
(196) 1-Ethyl-4-[3-(2-ethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(197) 1-(2-Hydroxyethyl)-4-[3-(2-ethylphenyl)-4-chloro-5-(1-fluoropropyl)]phenylpiperazin,
(198) 1-(2-Hydroxyethyl)-4-{3-(2-trifluoromethylphenyl)-4-chloro-5-[1-fluoropropyl]}phenylpiperazin,
(199) 1-Methyl-4-{3-(2-tolyl)-4-chloro-5-[1-fluoropropyl] }phenylpiperazin, und
(200) 1-(2-Hydroxyethyl)-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-[1-fluoropropyl]}phenylpiperazin.

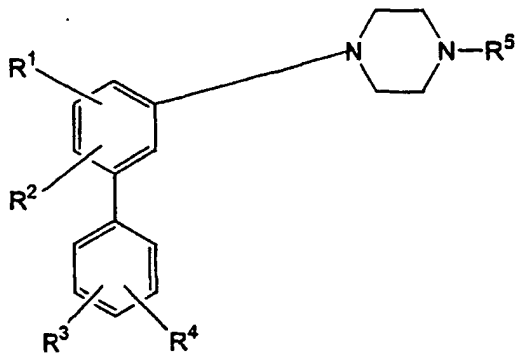
6. Ein therapeutisches oder verbesserndes Mittel für mentale Störungen, das eine Biphenylverbindung oder deren pharmakologisch akzeptables Salz gemäß Anspruch 1 als aktiven Bestandteil enthält.

7. Ein therapeutisches oder verbesserndes Mittel für mentale Störungen gemäß Anspruch 6, worin die mentale Störung zumindest eine ausgewählt aus der Gruppe bestehend aus zerebrovaskulären Störungen, aggressivem Verhalten aufgrund seniler Demenz, mentaler Aufregung, Poriomanie, Delirium, Halluzination, Hyperkinesie, Schizo-

phrenie, emotionaler Störung, Depression, Neurose, psycho-physiologischer Störung und Angstneurose ist.

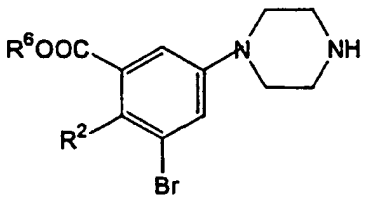
8. Ein therapeutisches oder verbesserndes Mittel für Krankheiten, gegen die ein Dopamin-2-Rezeptor-Antagonismus und/oder Serotonin-2-Rezeptor-Antagonismus wirksam ist, umfassend die Biphenylverbindung oder deren pharmakologisch akzeptables Salz gemäß Anspruch 1 als aktiven Bestandteil.

9. Verfahren zur Herstellung der Biphenylverbindung gemäß der folgenden Formel (I):



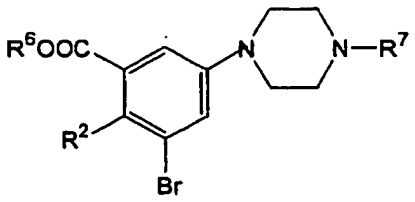
(I)

worin
R^1 eine halogenierte C_1-C_6-Alkylgruppe repräsentiert;
R^2 ein Wasserstoffatom, ein Halogenatom, eine Cyanogruppe, eine Hydroxylgruppe, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine C_1-C_6-Alkoxyalkylgruppe, eine C_1-C_6-Alkoxygruppe oder eine halogenierte C_1-C_6-Alkoxygruppe repräsentiert;
R^3 eine Cyanogruppe repräsentiert;
R^4 ein Wasserstoffatom, ein Halogenatom, eine C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, eine Hydroxyiminomethylgruppe oder eine Formylgruppe repräsentiert; und
R^5 eine Hydroxy-C_1-C_6-Alkylgruppe repräsentiert;
umfassend das Schützen einer durch die folgende Formel (III) dargestellten Phenylpiperazinverbindung:



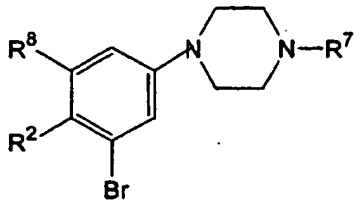
(III)

worin R^2 wie oben definiert ist und R^6 eine C_1-C_6-Alkylgruppe repräsentiert;
unter Bildung einer geschützten Phenylpiperazinverbindung, die durch die folgende Formel (IV) dargestellt ist:



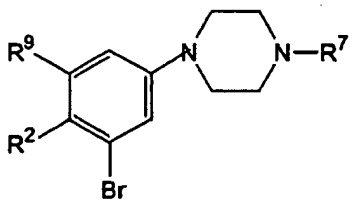
(IV)

worin R^2 und R^6 jeweils wie oben definiert sind, und R^7 eine Aminoschutzgruppe darstellt;
Umsetzen der Verbindung (IV) mit einem Alkylmagnesiumhalogenid unter Bildung einer geschützten Hydroxyalkylphenylpiperazinverbindung, die durch die folgende Formel (V) dargestellt ist:



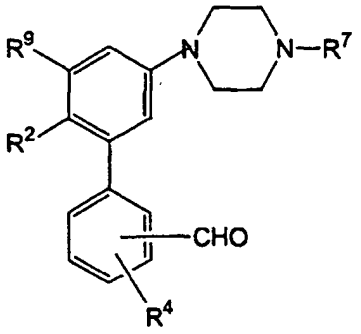
(V)

worin R^2 und R^7 jeweils wie oben definiert sind, und R^8 eine Hydroxyalkylgruppe repräsentiert;
Umsetzen der Verbindung (V) mit einem Halogenierungsmittel unter Bildung einer geschützten halogenierten Alkylphenylpiperazinverbindung, die durch die folgende Formel (VI) dargestellt ist:



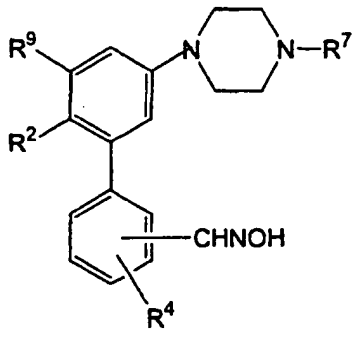
(VI)

worin R^2 und R^7 jeweils wie oben definiert sind; und R^9 eine halogenierte Alkylgruppe repräsentiert;
Umsetzen der Verbindung (VI) mit 2-(1,3,2-Dioxaborinan-2-yl)benzaldehyd in Gegenwart von Tetrakis(triphenylphosphin)palladium (0) und Cäsiumcarbonat unter Bildung einer geschützten halogenierten Alkylbiphenylpiperazinverbindung, die durch die folgende Formel (VIII) dargestellt ist.



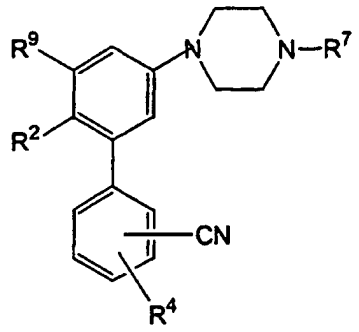
(VII)

worin R^2, R^4, R^7 und R^9 jeweils wie oben definiert sind;
Umsetzen der Verbindung (VII) mit Hydroxylamin unter Bildung einer geschützten halogenierten Alkyloximbiphenylpiperazinverbindung, die durch die folgende Formel (VIII) dargestellt ist:



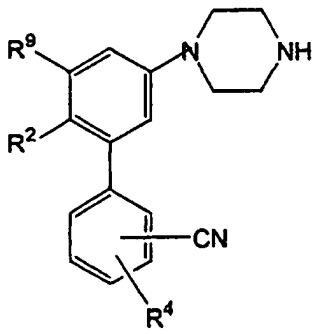
(VIII)

worin R^2, R^4, R^7 und R^9 jeweils wie oben definiert sind;
Umsetzen der Verbindung (VIII) mit Essigsäureanhydrid in Gegenwart von Pyridin und 4-Dimethylaminopyridin unter Bildung einer geschützten halogenierten Alkylcyanobiphenylpiperazinverbindung, die durch die folgende Formel (IX) dargestellt ist:



(IX)

worin R^2, R^4, R^7 und R^9 jeweils wie oben definiert sind;
Behandeln der Verbindung (IX) mit einer Säure unter Bildung einer halogenierten Alkylcyanobiphenylpiperazinverbindung, die durch die folgende Formel (X) dargestellt ist:

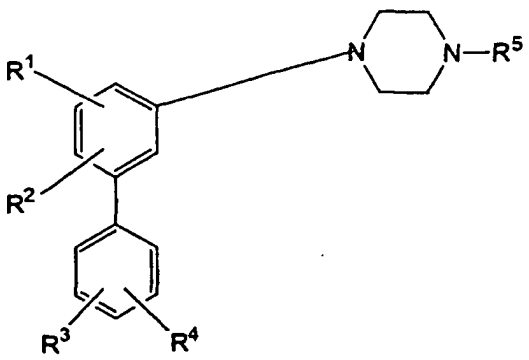


(X)

worin R^2, R^4 und R^9 jeweils wie oben definiert sind;
und Umsetzen der Verbindung (X) mit einem halogenierten Alkanol.

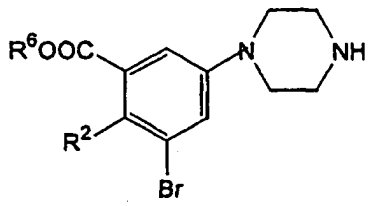
10. Verfahren gemäß Anspruch 9, worin das Halogenierungsmittel Diethylaminoschwefeltrifluorid ist.

11. Verfahren zur Herstellung einer Biphenylverbindung, die durch die folgende Formel (I) dargestellt ist:



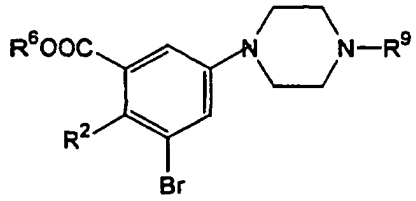
(I)

worin
R^1 eine C_1-C_6-Alkylsulfonylaminogruppe repräsentiert;
R^2 ein Halogenatom repräsentiert;
R^3 und R^4 dieselben sein können oder sich voneinander unterscheiden können und jeweils eine C_1-C_6-Alkylgruppe repräsentieren;
R^5 ein Wasserstoffatom, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, eine Heteroarylalkylgruppe, eine Aralkylgruppe, eine C_1-C_6-Alkoxycarbonylgruppe oder eine Aryloxycarbonylgruppe repräsentiert;
umfassend die Umsetzung einer Phenylpiperazinverbindung, die durch die folgende Formel (III) dargestellt ist:



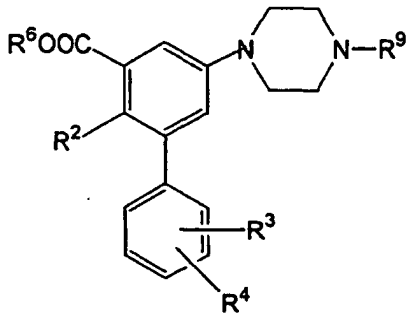
(III)

worin R^2 wie oben definiert ist und R^6 eine C_1-C_6-Alkylgruppe repräsentiert;
mit einem Alkylhalogenid unter Bildung einer Phenylalkylpiperazinverbindung, die durch die folgende Formel (XI) dargestellt ist:



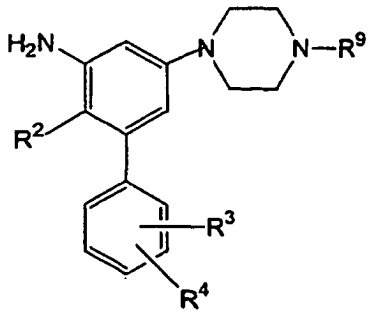
(XI)

worin R^2 und R^6 jeweils wie oben definiert sind und R^9 eine halogenierte Alkylgruppe repräsentiert;
Umsetzen der Verbindung (XI) mit Tolylborsäure in Gegenwart von Palladiumacetat unter Bildung einer Biphenylalkylpiperazinverbindung, die durch die folgende Formel (XII) dargestellt ist:



(XII)

worin R^2, R^3, R^4, R^6 und R^9 jeweils wie oben definiert sind;
Hydrolysieren der Verbindung (XII), Umsetzen des Produkts der Hydrolyse mit Ethylchlorocarbonat in Gegenwart einer Base, sukzessives Umsetzen des Produkts dieser Reaktion mit Natriumazid und einer Base unter Bildung einer Aminobiphenylalkylpiperazinverbindung, die durch die folgende Formel (XIII) dargestellt ist:

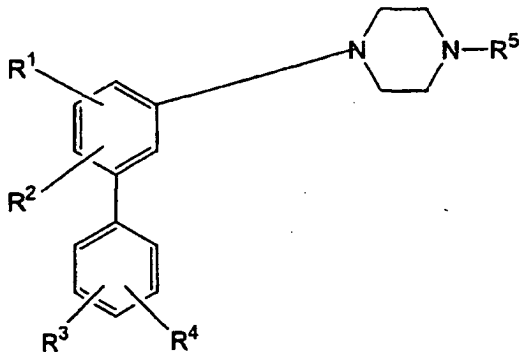


(XIII)

worin R^2, R^3, R^4 und R^9 jeweils wie oben definiert sind;
und Umsetzen der Verbindung (XIII) mit einem Alkylsulfonylhalogenid;
worin der Begriff Heteroarylgruppe eine Thienylgruppe, Furanylgruppe, Pyranylgruppe, Imidazolylgruppe, Thiazolylgruppe, Pyridylgruppe oder Pyrazylgruppe bezeichnet; der Begriff Heteroarylalkylgruppe eine Thienylmethylgruppe, Furfurylgruppe, Imidazolylmethylgruppe, Thiazolylmethylgruppe, Pyridylmethylgruppe oder Pyrazylmethylgruppe bezeichnet; und der Begriff halogenierte Heteroarylalkylgruppe eine wie oben definierte Heteroarylalkylgruppe bezeichnet, bei der zumindest ein Wasserstoffatom durch ein Halogenatom ersetzt ist; und worin der Begriff Arylgruppe eine unsubstituierte Arylgruppe, eine Tolylgruppe, eine Xylylgruppe, eine Methoxyphenylgruppe, eine Chlorophenylgruppe, eine Bromophenylgruppe, eine Fluorophenylgruppe, eine Nitrophenylgruppe oder eine Cyanophenylgruppe bezeichnet.

12. Verfahren gemäß Anspruch 11, worin die in der Reaktion des Hydrolyseprodukts mit Ethylchlorocarbonat verwendete Base Triethylamin ist.

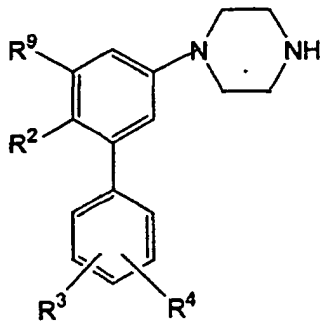
13. Verfahren zur Herstellung einer Biphenylverbindung, die durch die folgende Formel (I) dargestellt ist:



(I)

worin
R^1 ein Wasserstoffatom, ein Halogenatom, eine Hydroxylgruppe, eine Aminogruppe, eine Cyanogruppe, eine Pyrrolidylgruppe, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine Cyano-C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, eine Amino-C_1-C_6-Alkylgruppe, eine Cycloalkylgruppe, eine Cycloalkylalkylgruppe, eine C_1-C_6-Alkoxyalkylgruppe, eine Heteroarylalkylgruppe, eine halogenierte Heteroarylalkylgruppe, eine C_1-C_6-Acylalkylgruppe, eine Heteroarylalkoxyalkylgruppe, eine Cycloalkyloxyalkylgruppe, eine Aralkyloxyalkylgruppe, eine Alkenyloxyalkylgruppe, eine C_1-C_6-Alkoxycarbonylalkylgruppe, eine C_1-C_6-Alkoxyalkoxyalkylgruppe, eine Arylhydroxyalkylgruppe, eine Hydroxyheteroarylalkylgruppe, eine Cycloalkylalkoxyalkylgruppe, eine Alkenylgruppe, eine halogenierte Alkenylgruppe, eine Alkynylgruppe, eine Aralkylgruppe, eine halogenierte Aralkylgruppe, eine Hydroxyaralkylgruppe, eine halogenierte Hydroxyiminoaralkylgruppe, eine C_1-C_6-Alkoxygruppe, eine halogenierte C_1-C_6-Alkoxygruppe, eine C_1-C_6-Alkoxyalkoxygruppe, eine Arylgruppe, eine Hydroxyarylgruppe, eine halogenierte Arylgruppe, eine C_1-C_6-Alkoxyarylgruppe, eine Heteroarylgruppe, eine Hydroxyheteroarylgruppe, eine halogenierte Heteroarylgruppe, eine C_1-C_6-Alkoxyheteroarylgruppe, eine Formylgruppe, eine C_1-C_6-Acylgruppe, eine aromatische Acylgruppe, eine heteroaromatische Acylgruppe, eine Aralkylcarbonylgruppe, eine Cycloalkylalkyl-

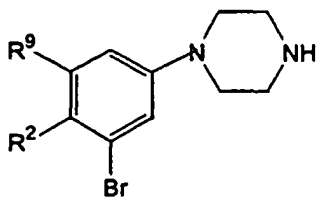
carbonylgruppe, eine Heteroarylalkylcarbonylgruppe, eine halogenierte Aralkylcarbonylgruppe, eine C_1-C_6-Alkoxycarbonylgruppe, eine Aryloxycarbonylgruppe, eine C_1-C_6-Alkylaminogruppe, eine C_1-C_6-Alkylsulfonylaminogruppe, eine halogenierte C_1-C_6-Alkylsulfonylaminogruppe, eine Arylsulfonylaminogruppe, eine halogenierte Arylsulfonylaminogruppe, eine Aralkylsulfonylaminogruppe, eine Cycloethergruppe, eine zyklische C_1-C_6-Acetalgruppe, eine zyklische C_1-C_6-Thioacetalgruppe, eine C_1-C_6-Alkylsulfinylgruppe, eine Arylsulfinylgruppe, eine Aralkylsulfinylgruppe, eine Heteroarylsulfinylgruppe, eine C_1-C_6-Alkylsulfonylgruppe, eine Arylsulfonylgruppe, eine Aralkylsulfonylgruppe, eine Heteroarylsulfonylgruppe, eine Cycloalkylsulfonylgruppe, eine Aminosulfonylgruppe, eine C_1-C_6-Alkylaminosulfonylgruppe, eine Arylaminosulfonylgruppe, eine Pyrrolidylsulfonylgruppe, eine Cycloalkylaminosulfonylgruppe, eine halogenierte C_1-C_6-Alkylsulfonylgruppe, eine halogenierte Aryloxy-C_1-C_6-Alkylsulfonylgruppe oder eine Cyano-C_1-C_6-Alkylsulfonylgruppe repräsentiert;
R^2 und R^3 können dieselben sein oder sich voneinander unterscheiden und jeweils ein Wasserstoffatom, ein Halogenatom, eine Cyanogruppe, eine Hydroxylgruppe, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine C_1-C_6-Alkoxyalkylgruppe, eine C_1-C_6-Alkoxygruppe oder eine halogenierte C_1-C_6-Alkoxygruppe oder eine halogenierte C_1-C_6-Alkoxygruppe repräsentieren;
R^4 repräsentiert ein Wasserstoffatom, ein Halogenatom, eine C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, eine Hydroxyiminomethylgruppe oder eine Formylgruppe;
R^5 repräsentiert ein Wasserstoffatom, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, eine Heteroarylalkylgruppe, eine Aralkylgruppe, eine C_1-C_6-Alkoxycarbonylgruppe oder eine Aryloxycarbonylgruppe;
umfassend die Umsetzung einer Biphenylpiperazinverbindung, die durch die folgende Formel (XXI) dargestellt ist:



(XXI)

worin R^2, R^3 und R^4 jeweils wie oben definiert sind und R^9 eine halogenierte Alkylgruppe repräsentiert;
mit einer aktiven durch die Formel R^5L (worin R^5 wie oben definiert ist und L eine Abgangsgruppe repräsentiert) dargestellten Verbindung;
worin der Begriff Heteroarylgruppe eine Thienylgruppe, Furanylgruppe, Pyranylgruppe, Imidazolylgruppe, Thiazolylgruppe, Pyridylgruppe oder Pyrazylgruppe bezeichnet; der Begriff Heteroarylalkylgruppe eine Thienylmethylgruppe, Furfurylgruppe, Imidazolylmethygruppe, Thiazolylmethylgruppe, Pyridylmethylgruppe oder Pyrazylmethylgruppe bezeichnet; und der Begriff halogenierte Heteroarylalkylgruppe eine wie oben definierte Heteroarylalkylgruppe bezeichnet, bei der zumindest ein Wasserstoffatom durch ein Halogenatom ersetzt ist; und worin der Begriff Arylgruppe eine unsubstituierte Arylgruppe, eine Tolylgruppe, eine Xylylgruppe, eine Methoxyphenylgruppe, eine Chlorophenylgruppe, eine Bromophenylgruppe, eine Fluorophenylgruppe, eine Nitrophenylgruppe oder eine Cyanophenylgruppe bezeichnet.

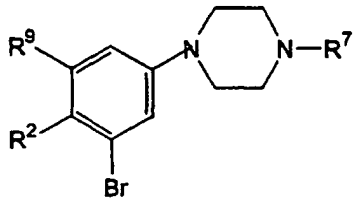
14. Verfahren gemäß Anspruch 13, weiterhin umfassend die Umsetzung einer halogenierten Alkylphenylpiperazinverbindung, die durch die folgende Formel (XX) dargestellt ist:



(XX)

worin R^2 wie oben definiert ist und R^9 eine halogenierte Alkylgruppe repräsentiert;
mit einer 2-(1,3,2-dioxaborinan-2-yl)benzolverbindung oder einer Phenylborsäureverbindung in Gegenwart von Triphenylphosphinpalladium und Trikaliumphosphat unter Bildung einer Biphenylpiperazinverbindung, die durch die obige Formel (XXI) dargestellt ist.

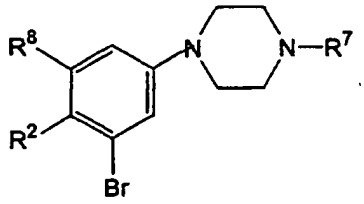
15. Verfahren gemäß Anspruch 14, weiterhin umfassend die Entschützung einer geschützten halogenierten Alkylphenylpiperazinverbindung, die durch die folgende Formel (VI) dargestellt ist:



(VI)

worin R^2 und R^9 jeweils wie oben definiert sind; und R^7 eine Aminoschutzgruppe repräsentiert;
unter Bildung einer halogenierten Alkylphenylpiperazinverbindung, die durch die obige Formel (XX) dargestellt ist.

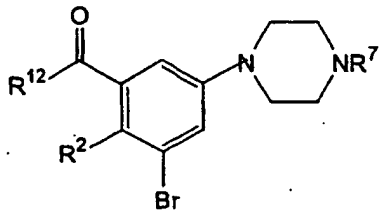
16. Verfahren gemäß Anspruch 15, weiterhin umfassend die Umsetzung einer geschützten Hydroxyalkylphenylpiperazinverbindung, die durch die folgende Formel (V) dargestellt ist:



(V)

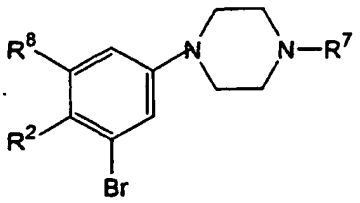
worin R^2 und R^7 jeweils wie oben definiert sind, und R^8 eine Hydroxyalkylgruppe repräsentiert;
mit einem Halogenierungsmittel unter Bildung einer geschützten halogenierten Alkylphenylpiperazinverbindung, die durch die obige Formel (VI) dargestellt ist.

17. Verfahren gemäß Anspruch 15, weiterhin umfassend die Reduzierung einer geschützten Acylphenylpiperazinverbindung, die durch die folgende Formel (XXIII) dargestellt ist:



(XXIII)

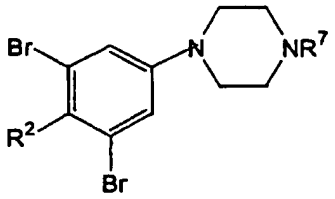
worin R^2 und R^7 jeweils wie oben definiert sind; und R^{12} eine C_1-C_6-Alkylgruppe repräsentiert,
in eine geschützte Hydroxyalkylphenylpiperazinverbindung, die durch die folgende Formel (V) dargestellt ist:



(V)

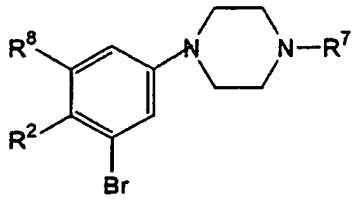
worin R^2 und R^7 jeweils wie oben definiert sind, und R^8 eine Hydroxyalkylgruppe repräsentiert;
und Umsetzung der Verbindung (V) mit einem Halogenierungsmittel unter Bildung einer geschützten halogenierten Alkylphenylpiperazinverbindung, die durch die obige Formel (VI) dargestellt ist.

18. Verfahren gemäß Anspruch 15, weiterhin umfassend die Umsetzung einer geschützten Dibromophenylpiperazinverbindung, die durch die folgende Formel (XXVI) dargestellt ist:



(XXVI)

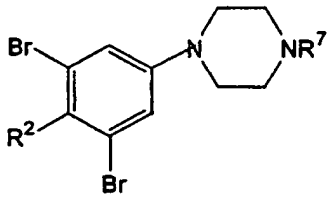
worin R^2 und R^7 jeweils wie oben definiert sind,
mit einem C_1-C_6 aliphatischen Aldehyd in Gegenwart einer Base unter Bildung einer geschützten Hydroxyalkylphenylpiperazinverbindung, die durch die folgende Formel (V) dargestellt ist:



(V)

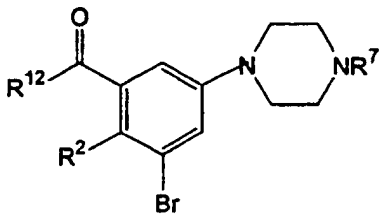
worin R^2 und R^7 jeweils wie oben definiert sind, und R^8 eine Hydroxyalkylgruppe repräsentiert;
und Umsetzung der Verbindung (V) mit einem Halogenierungsmittel unter Bildung einer geschützten halogenierten Alkylphenylpiperazinverbindung, die durch die obige Formel (VI) dargestellt ist.

19. Verfahren gemäß Anspruch 15, weiterhin umfassend die Umsetzung einer geschützten Dibromophenylpiperazinverbindung, die durch die folgende Formel (XXVI) dargestellt ist:



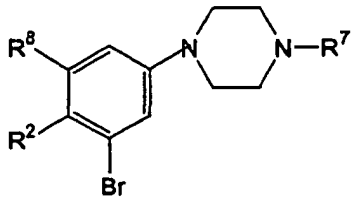
(XXVI)

worin R^2 und R^7 jeweils wie oben definiert sind,
mit einem Säureanhydrid in Gegenwart einer Base unter Bildung einer geschützten Acylphenylpiperazinverbindung, die durch die folgende Formel (XXIII) dargestellt ist:



(XXIII)

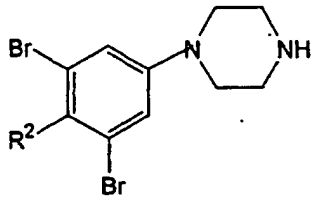
worin R^2 und R^7 jeweils wie oben definiert sind; und R^{12} eine C_1-C_6-Alkylgruppe repräsentiert,
Reduzieren der Verbindung (XXIII) in eine geschützte Hydroxyalkylphenylpiperazinverbindung, die durch die folgende Formel (V) dargestellt ist:



(V)

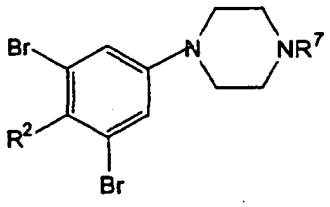
worin R^2 und R^7 jeweils wie oben definiert sind, und R^8 eine Hydroxyalkylgruppe repräsentiert;
und Umsetzung der Verbindung (V) mit einem Halogenierungsmittel unter Bildung einer geschützten halogenierten Alkylphenylpiperazinverbindung, die durch die obige Formel (VI) dargestellt ist.

20. Verfahren gemäß Anspruch 15, weiterhin umfassend die Schützung einer Dibromophenylpiperazinverbindung, die durch die folgende Formel (XXV) dargestellt ist:



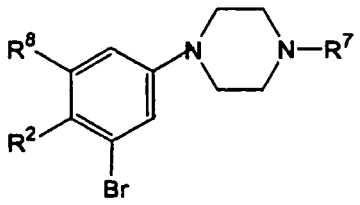
(XXV)

worin R^2 wie oben definiert ist,
unter Bildung einer geschützten Dibromophenylpiperazinverbindung, die durch die folgende Formel (XXVI) dargestellt ist:



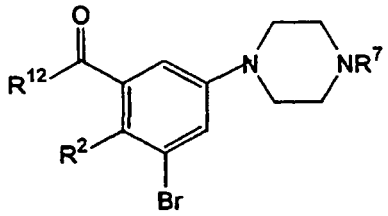
(XXVI)

worin R^2 und R^7 jeweils wie oben definiert sind,
Überführen der Verbindung (XXVI) in eine geschützte Hydroxyalkylphenylpiperazinverbindung, die durch die folgende Formel (V) dargestellt ist.



(V)

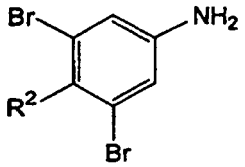
worin R^2 und R^7 jeweils wie oben definiert sind, und R^8 eine Hydroxyalkylgruppe repräsentiert;
entweder durch Umsetzung der Verbindung (XXVI) mit einem C_1-C_6 aliphatischen Aldehyd in Gegenwart einer Base oder durch Umsetzung der Verbindung (XXVI) mit einem Säureanhydrid in Gegenwart einer Base unter Bildung einer geschützten Acylphenylpiperazinverbindung, die durch die folgende Formel (XXIII) dargestellt ist:



(XXIII)

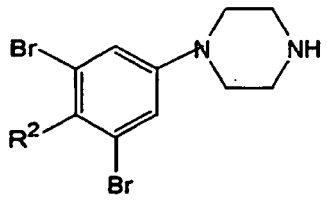
worin R^2 und R^7 jeweils wie oben definiert sind; und R^{12} eine C_1-C_6-Alkylgruppe repräsentiert,
und Reduzieren der Verbindung (XXIII) und Umsetzen der Verbindung (V) mit einem Halogenierungsmittel unter Bildung einer geschützten halogenierten Alkylphenylpiperazinverbindung, die durch die obige Formel (VI) dargestellt ist.

21. Verfahren gemäß Anspruch 15, weiterhin umfassend die Umsetzung einer Dibromoanilinverbindung, die durch die folgende Formel (XXIV) dargestellt ist:



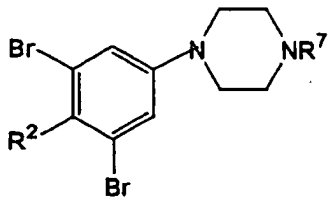
(XXIV)

worin R^2 wie oben definiert ist,
mit Bis(2-Chloroethyl)amin unter Bildung einer Dibromophenylpiperazinverbindung, die durch die folgende Formel (XXV) dargestellt ist:



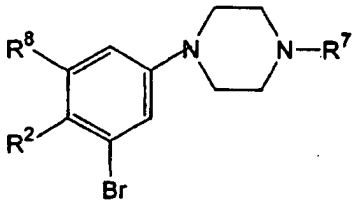
(XXV)

worin R^2 wie oben definiert ist,
Schützung der Verbindung (XXV) unter Bildung einer geschützten Dibromophenylpiperazinverbindung, die durch die folgende Formel (XXVI) dargestellt ist:



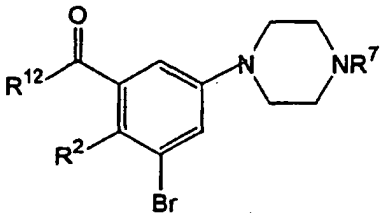
(XXVI)

worin R^2 und R^7 jeweils wie oben definiert sind,
Überführen der Verbindung (XXVI) in eine geschützte Hydroxyalkylphenylpiperazinverbindung, die durch die folgende Formel (V) dargestellt ist:



(V)

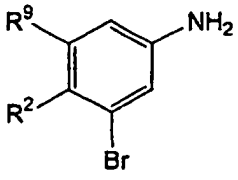
worin R^2 und R^7 jeweils wie oben definiert sind, und R^8 eine Hydroxyalkylgruppe repräsentiert;
entweder durch Umsetzen der Verbindung (XXVI) mit einem C_1-C_6 aliphatischen Aldehyd in Gegenwart einer Base oder durch Umsetzen der Verbindung (XXVI) mit einem Säureanhydrid in Gegenwart einer Base unter Bildung einer geschützten Acylphenylpiperazinverbindung, die durch die folgende Formel (XXIII) dargestellt ist:



(XXIII)

worin R^2 und R^7 jeweils wie oben definiert sind; und R^{12} eine C_1-C_6-Alkylgruppe repräsentiert,
und Reduzieren der Verbindung (XXIII) und Umsetzen der Verbindung (V) mit einem Halogenierungsmittel unter Bildung einer geschützten halogenierten Alkylphenylpiperazinverbindung, die durch die obige Formel (VI) dargestellt ist.

22. Verfahren gemäß Anspruch 14, weiterhin umfassend die Umsetzung einer halogenierten Alkylanilinverbindung, die durch die folgende Formel (XIX) dargestellt ist:

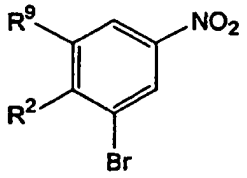


(XIX)

worin R^2 und R^9 jeweils wie oben definiert sind,
mit Bis(2-chloroethyl)amin unter Bildung einer halogenierten Alkylphenylpiperazinverbindung, die durch die obige Formel (XX) dargestellt ist.

23. Verfahren gemäß Anspruch 22, weiterhin umfassend die Reduzierung einer halogenierten Alkylnitrobenzolverbin-

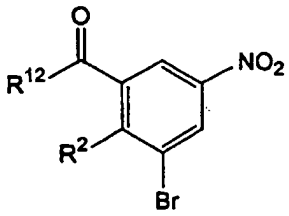
dung, die durch die folgende Formel (XVIII) dargestellt ist:



(XVIII)

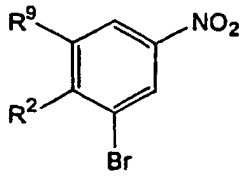
worin R^2 und R^9 jeweils wie oben definiert sind,
in eine halogenierte Alkylanilinverbindung, die durch die obige Formel (XIX) dargestellt ist.

24. Verfahren gemäß Anspruch 22, weiterhin umfassend die Reduzierung einer Acylnitrobenzolverbindung, die durch die folgende Formel (XVII) dargestellt ist:



(XVII)

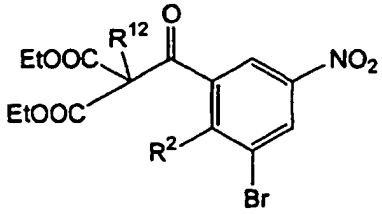
worin R^2 wie oben definiert ist und R^{12} eine C_1-C_6-Alkylgruppe repräsentiert,
Umsetzen des Produkts der Reduktion mit einem Halogenierungsmittel unter Bildung einer halogenierten Alkylnitrobenzolverbindung, die durch die folgende Formel (XVIII) dargestellt ist:



(XVIII)

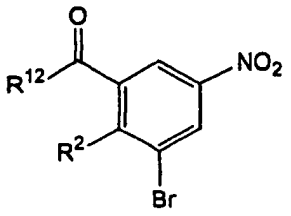
worin R^2 und R^9 jeweils wie oben definiert sind,
und Reduzieren der Verbindung (XVIII) in eine halogenierte Alkylanilinverbindung, die durch die obige Formel (XIX) dargestellt ist.

25. Verfahren gemäß Anspruch 22, weiterhin umfassend die Umsetzung einer Malonsäureesterverbindung, die durch die folgende Formel (XVI) dargestellt ist:



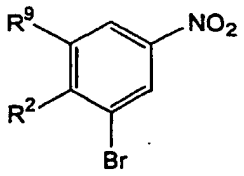
(XVI)

worin R^2 wie oben definiert ist und R^{12} eine C_1-C_6-Alkylgruppe repräsentiert,
mit einer Säure oder einer Base unter Bildung einer Acylnitrobenzolverbindung, die durch die folgende Formel (XVII) dargestellt ist:



(XVII)

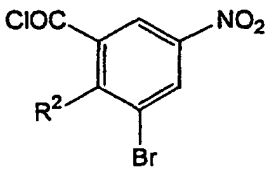
worin R^2 und R^{12} jeweils wie oben definiert sind,
Reduzieren der Verbindung (XVII), Umsetzen des Produkts der Reduzierung mit einem Halogenierungsmittel unter Bildung einer halogenierten Alkylnitrobenzolverbindung, die durch die folgende Formel (XVIII) dargestellt ist:



(XVIII)

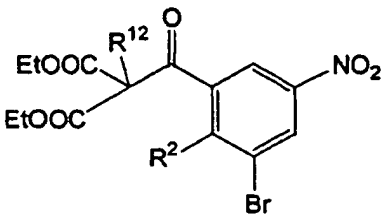
worin R^2 und R^9 jeweils wie oben definiert sind,
und Reduzieren der Verbindung (XVIII) in eine halogenierte Alkylanilinverbindung, die durch die obige Formel (XIX) dargestellt ist.

26. Verfahren gemäß Anspruch 22, weiterhin umfassend die Umsetzung einer Nitrobenzoylchloridverbindung, die durch die folgende Formel (XV) dargestellt ist:



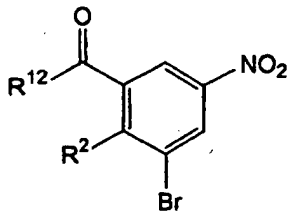
(XV)

worin R^2 wie oben definiert ist,
mit einem Alkylmalonsäureester in Gegenwart einer Base unter Bildung einer Malonsäureesterverbindung, die durch die folgende Formel (XVI) dargestellt ist:



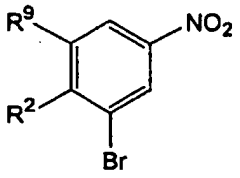
(XVI)

worin R^2 wie oben definiert ist und R^{12} eine C_1-C_6-Alkylgruppe repräsentiert,
Umsetzung der Verbindung (XVI) mit einer Säure oder einer Base unter Bildung einer Acylnitrobenzolverbindung, die durch die folgende Formel (XVII) dargestellt ist:



(XVII)

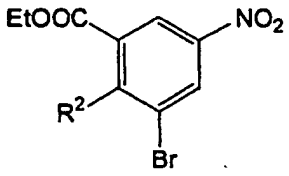
worin R^2 und R^{12} jeweils wie oben definiert sind,
Reduzierung der Verbindung (XVII), Umsetzung des Produkts der Reduzierung mit einem Halogenierungsmittel unter Bildung einer halogenierten Alkylnitrobenzolverbindung, die durch die folgende Formel (XVIII) dargestellt ist:



(XVIII)

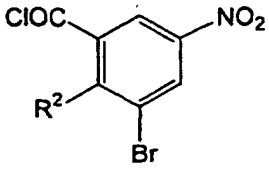
worin R^2 und R^9 jeweils wie oben definiert sind,
und Reduzierung der Verbindung (XVIII) in eine halogenierte Alkylanilinverbindung, die durch die obige Formel (XIX) dargestellt ist.

27. Verfahren gemäß Anspruch 22, weiterhin umfassend die Hydrolysierung einer Nitrobenzoesäureesterverbindung, die durch die folgende Formel (XIV) dargestellt ist:



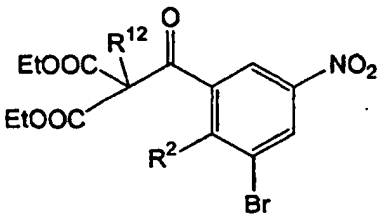
(XIV)

worin R^2 wie oben definiert ist,
Umsetzung des Produkts der Hydrolyse mit einem Chlorierungsmittel unter Bildung einer Nitrobenzoylchloridverbindung, die durch die folgende Formel (XV) dargestellt ist:



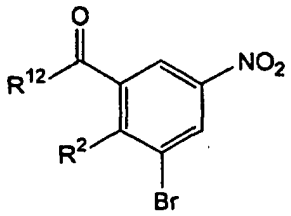
(XV)

worin R^2 wie oben definiert ist,
Umsetzung der Verbindung (XV) mit einem Alkylmalonsäureester in Gegenwart einer Base unter Bildung einer Malonsäureesterverbindung, die durch die folgende Formel (XVI) dargestellt ist:



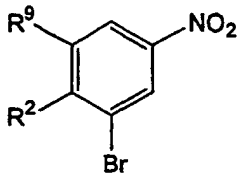
(XVI)

worin R^2 wie oben definiert ist und R^{12} eine C_1-C_6-Alkylgruppe repräsentiert,
Umsetzen der Verbindung (XVI) mit einer Säure oder einer Base unter Bildung einer Acylnitrobenzolverbindung, die durch die folgende Formel (XVII) dargestellt ist:



(XVII)

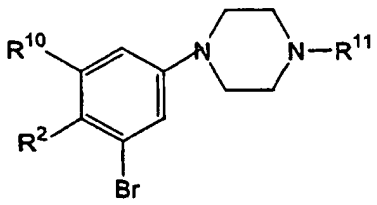
worin R^2 und R^{12} jeweils wie oben definiert sind, Reduzieren der Verbindung (XVII), Umsetzen des Produkts der Reduzierung mit einem Halogenierungsmittel unter Bildung einer halogenierten Alkylnitrobenzolverbindung, die durch die folgende Formel (XVIII) dargestellt ist:



(XVIII)

worin R^2 und R^9 jeweils wie oben definiert sind,
und Reduzierung der Verbindung (XVIII) in eine halogenierte Alkylanilinverbindung, die durch die obige Formel (XIX) dargestellt ist.

28. Eine Phenylpiperazinverbindung, die durch die folgende allgemeine Formel (XXVII) dargestellt ist oder dessen Salz:



(XXVII)

worin
R^2 ein Wasserstoffatom, ein Halogenatom, eine Cyanogruppe, eine Hydroxylgruppe, eine C_1-C_6-Alkylgrupe, eine halogenierte C_1-C_6-Alkylgruppe, eine C_1-C_6-Alkoxygruppe oder eine halogenierte C_1-C_6-Alkoxygruppe repräsentiert;
R^{10} repräsentiert eine halogenierte C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, ein Halogenatom, eine C_1-C_6-Alkylsulfonylgruppe, eine C_1-C_6-Alkoxycarbonylgruppe, eine Carboxylgruppe, eine Alkenylgruppe, eine

(Pyridyl-thio)carbonylgruppe oder eine C_1-C_6-Acylgruppe; und
R^{11} repräsentiert ein Wasserstoffatom, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine Hydroxy-C_1-C_6-Alkylgruppe, eine Tri(C_1-C_6alkyl)silyloxy-C_1-C_6-alkylgruppe, eine heteroarylalkylgruppe, eine Aralkylgruppe, eine C_1-C_6-Alkoxycarbonylgruppe, eine Aryloxycarbonylgruppe oder eine Aminoschutzgruppe;
worin der Begriff Heteroarylgruppe eine Thienylgruppe, Furanylgruppe, Pyranylgruppe, Imidazolylgruppe, Thiazolylgruppe, Pyridylgruppe oder Pyrazylgruppe bezeichnet; der Begriff Heteroarylalkylgruppe eine Thienylmethylgruppe, Furfurylgruppe, Imidazolylmethylgruppe, Thiazolylmethylgruppe, Pyridylmethylgruppe oder Pyrazylmethylgruppe bezeichnet; und der Begriff halogenierte Heteroarylalkylgruppe eine wie oben definierte Heteroarylalkylgruppe bezeichnet, bei der zumindest ein Wasserstoffatom durch ein Halogenatom ersetzt ist; und worin der Begriff Arylgruppe eine unsubstituierte Arylgruppe, eine Tolylgruppe, eine Xylylgruppe, eine Methoxyphenylgruppe, eine Chlorophenylgruppe, eine Bromophenylgruppe, eine Fluorophenylgruppe, eine Nitrophenylgruppe oder eine Cyanophenylgruppe bezeichnet.

29. Phenylpiperazinverbindung oder deren Salz gemäß Anspruch 28, worin R^2 wie oben definiert ist; R^{10} repräsentiert eine halogenierte C_1-C_6-Alkylgruppe oder eine Hydroxy-C_1-C_6-Alkylgruppe; und R^{11} repräsentiert ein Wasserstoffatom, eine Hydroxy-C_1-C_6-Alkylgruppe oder eine Aminoschutzgruppe.

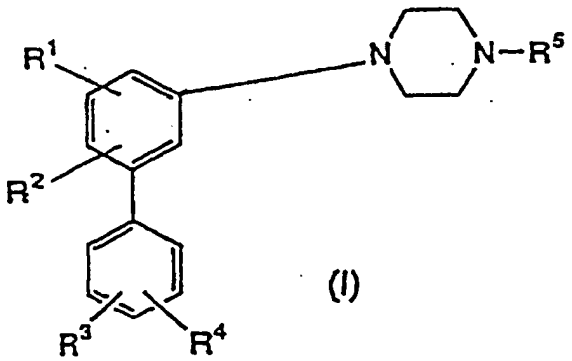
30. Phenylpiperazinverbindung oder deren Salz gemäß Anspruch 29, worin R^2 ein Wasserstoffatom, ein Halogenatom, eine C_1-C_6-Alkylgruppe, eine halogenierte C_1-C_6-Alkylgruppe, eine C_1-C_6-Alkoxygruppe, eine halogenierte C_1-C_6-Alkoxygruppe oder eine Cyanogruppe repräsentiert; und R^{10} und R^{11} jeweils wie oben definiert sind.

31. Eine pharmazeutische Zusammensetzung umfassend eine Biphenylverbindung oder deren pharmakologisch akzeptables Salz gemäß Anspruch 1 in einer therapeutisch oder verbessernd wirkenden Menge und einen pharmakologisch akzeptablen Träger.

32. Verwendung einer Biphenylverbindung oder deren pharmakologisch akzeptablen Salzes gemäß Anspruch 1 zur Herstellung eines Medikaments zur Behandlung oder Verbesserung einer Krankheit, gegen die Dopamin-2-Rezeptor-Antagonismus und/oder Serotonin-2-Rezeptor-Antagonismus wirksam sind.

Revendications

1. Dérivé de biphényle représenté par la formule (I) suivante ou sel de celui-ci pharmacologiquement acceptable :



(I)

dans laquelle R^1 représente un atome d'hydrogène, un atome d'halogène, un groupement hydroxyle, un groupement amino, un groupement cyano, un groupement pyrrolidyle, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement cyanoalkyle en C_1 à C_6, un groupement hydroxyalkyle en C_1 à C_6, un groupement aminoalkyle en C_1 à C_6, un groupement cycloalkyle, un groupement cycloalkylalkyle, un groupement alcoxy (en C_1 à C_6) alkyle, un groupement hétéroarylalkyle, un groupement hétéroarylalkyle halogéné, un groupement acyl (en C_1 à C_6) alkyle, un groupement hétéroarylalcoxyalkyle, un groupement cycloalkyloxyalkyle, un groupement aralkyloxyalkyle, un groupement alcényloxyalkyle, un groupement alcoxy (en C_1 à C_6) carbonylalkyle, un groupement alcoxy (en C_1 à C_6) alcoxyalkyle, un groupement arylhydroxyalkyle, un groupement hydroxyhétéroarylalkyle, un groupement cycloalkylalcoxyalkyle, un groupement alcényle, un groupement alcényle

halogéné, un groupement alcynyle, un groupement aralkyle, un groupement aralkyle halogéné, un groupement hydroxyaralkyle, un groupement hydroxyiminoaralkyle halogéné, un groupement alcoxy en C_1 à C_6, un groupement alcoxy en C_1 à C_6 halogéné, un groupement alcoxy (en C_1 à C_6) alcoxy, un groupement aryle, un groupement hydroxyaryle, un groupement aryle halogéné, un groupement alcoxy (en C_1 à C_6) aryle, un groupement hétéroaryle, un groupement hydroxyhétéroaryle, un groupement hétéroaryle halogéné, un groupement alcoxy (en C_1 à C_6) hétéroaryle, un groupement formyle, un groupement acyle en C_1 à C_6, un groupement acyle aromatique, un groupement acyle hétéroaromatique, un groupement aralkylcarbonyle, un groupement cycloalkylalkylcarbonyle, un groupement hétéroarylalkylcarbonyle, un groupement aralkylcarbonyle halogéné, un groupement alcoxy (en C_1 à C_6) carbonyle, un groupement aryloxycarbonyle, un groupement alkylamino en C_1 à C_6, un groupement alkylsulfonylamino en C_1 à C_6, un groupement alkylsulfonylamino en C_1 à C_6 halogéné, un groupement arylsulfonylamino, un groupement arylsulfonylamino halogéné, un groupement aralkylsulfonylamino, un groupement cycloéther, un groupement acétal cyclique en C_1 à C_6, un groupement thioacétal cyclique en C_1 à C_6, un groupement alkylsulfinyle en C_1 à C_6, un groupement arylsulfinyle, un groupement aralkylsulfinyle, un groupement hétéroarylsulfinyle, un groupement alkylsulfonyle en C_1 à C_6, un groupement arylsulfonyle, un groupement aralkylsulfonyle, un groupement hétéroarylsulfonyle, un groupement cycloalkylsulfonyle, un groupement aminosulfonyle, un groupement alkylaminosulfonyle en C_1 à C_6, un groupement arylaminosulfonyle, un groupement pyrrolidylsulfonyle, un groupement cycloalkylaminosulfonyle, un groupement alkylsulfonyle en C_1 à C_6 halogéné, un groupement aryloxyalkyl (en C_1 à C_6) sulfonyle halogéné ou un groupement cyanoalkyl (en C_1 à C_6) sulfonyle,

R^2 et R^3 peuvent être identiques ou différents l'un de l'autre et chacun représente un atome d'hydrogène, un atome d'halogène, un groupement cyano, un groupement hydroxyle, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement alcoxy (en C_1 à C_6) alkyle, un groupement alcoxy en C_1 à C_6 ou un groupement alcoxy en C_1 à C_6 halogéné,

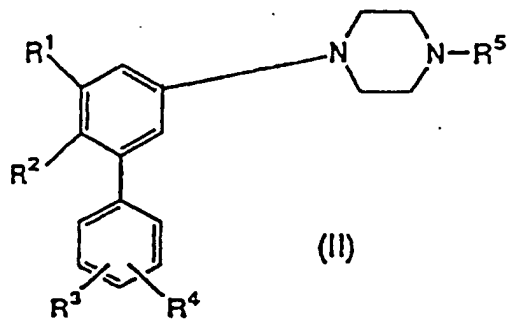
R^4 représente un atome d'hydrogène, un atome d'halogène, un groupement alkyle en C_1 à C_6, un groupement hydroxyalkyle en C_1 à C_6, un groupement hydroxyiminométhyle ou un groupement formyle,

R^5 représente un atome d'hydrogène, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement hydroxyalkyle en C_1 à C_6, un groupement hétéroarylalkyle, un groupement alcoxy (en C_1 à C_6) carbonyle ou un groupement aryloxycarbonyle,

à condition que le dérivé de biphényle ne soit ni la 1-[(3-phényl-4-méthyl)-phényl]pipérazine ni la 1-méthyl-4-[(3-phényl-4-méthyl)-phényl]pipérazine, et à condition que R^5 ne représente pas un atome d'hydrogène si R^1 et R^2 représentent des atomes d'hydrogène, R^3 représente un atome d'hydrogène, un atome d'halogène ou un groupement hydroxyle et si R^4 représente un atome d'hydrogène, un atome d'halogène ou un groupement formyle,

où l'expression groupement hétéroaryle indique un groupement thiényle, un groupement furanyle, un groupement pyranyle, un groupement imidazolyle, un groupement thiazolyle, un groupement pyridyle ou un groupement pyrazyle, l'expression groupement hétéroarylalkyle indique un groupement thiénylméthyle, un groupement furfuryle, un groupement imidazolylméthyle, un groupement thiazolylméthyle, un groupement pyridylméthyle ou un groupement pyrazylméthyle, l'expression groupement hétéroarylalkyle halogéné indique un groupement hétéroarylalkyle comme défini ci-dessus dans lequel au moins un atome d'hydrogène est remplacé par un atome d'halogène, et où l'expression groupement aryle indique un groupement aryle non substitué, un groupement tolyle, un groupement xylyle, un groupement méthoxyphényle, un groupement chlorophényle, un groupement bromophényle, un groupement fluorophényle, un groupement nitrophényle ou un groupement cyanophényle.

2. Dérivé de biphényle ou sel de celui-ci pharmacologiquement acceptable selon la revendication 1, où le dérivé de biphényle est représenté par la formule (II) suivante :



(II)

dans laquelle R^1, R^2, R^3, R^4 et R^5 sont chacun comme définis ci-dessus.

3. Dérivé de biphényle ou sel de celui-ci pharmacologiquement acceptable selon la revendication 1,

dans lequel R^1, représente un atome d'hydrogène, un atome d'halogène, un groupement hydroxyle, un groupement amino, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement alcoxy en C_1 à C_6, un groupement alcoxy en C_1 à C_6 halogéné, un groupement alcoxy (en C_1 à C_6) alkyle, un groupement alcoxy (en C_1 à C_6) alcoxy, un groupement aryle, un groupement aralkyle, un groupement hétéroaryle, un groupement hétéroarylalkyle, un groupement hétéroarylalkyle halogéné, un groupement cyanoalkyle en C_1 à C_6, un groupement hydroxyalkyle en C_1 à C_6, un groupement aminoalkyle en C_1 à C_6, un groupement alcoxy (en C_1 à C_6) carbonyle, un groupement aryloxycarbonyle, un groupement cyano, un groupement formyle, un groupement acyle en C_1 à C_6, un groupement aralkylcarbonyle, un groupement cycloéther, un groupement alcényle, un groupement alcylnyle, un groupement alkylsulfinyle en C_1 à C_6, un groupement alkylsulfonyle en C_1 à C_6, un groupement alkylaminosulfonyle en C_1 à C_6, un groupement arylaminosulfonyle, un groupement alkylsulfonylamino en C_1 à C_6, un groupement alkylsulfonylamino en C_1 à C_6 halogéné ou un groupement arylsulfonylamino,

R^2 et R^3 peuvent être identiques ou différents l'un de l'autre et chacun représente un atome d'hydrogène, un atome d'halogène, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement alcoxy en C_1 à C_6, un groupement alcoxy en C_1 à C_6 halogéné ou un groupement cyano,

R^4 représente un atome d'hydrogène ou un atome d'halogène,

R^5 représente un atome d'hydrogène, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement hydroxyalkyle en C_1 à C_6, un groupement alcoxy (en C_1 à C_6) carbonyle ou un groupement aryloxycarbonyle.

4. Dérivé de biphényle ou sel de celui-ci pharmacologiquement acceptable selon la revendication 1, dans lequel R^1 est un groupement alkyle en C_1 à C_6 halogéné ou un groupement alkylsulfonylamino en C_1 à C_6, R^2 est un atome d'halogène ou un groupement alcoxy en C_1 à C_6, R^3 est un atome d'halogène, un groupement alkyle en C_1 à C_6 ou un groupement cyano, R^4 est un atome d'hydrogène ou un atome d'halogène, R^5 est un atome d'hydrogène, un groupement alkyle en C_1 à C_6 ou un groupement hydroxyalkyle en C_1 à C_6.

5. Dérivé de biphényle ou sel de celui-ci pharmacologiquement acceptable selon la revendication 1, lequel est un composé choisi parmi le groupe constitué de

(1) la 1-[3-(2-cyanophényl)-4-chloro-5-(1-fluoropropyl)] phénylpipérazine,
(2) la 1-(2-hydroxyéthyl)-4-[3-(2-cyanophényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(3) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-éthoxycarbonyl] phénylpipérazine,
(4) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-amino] phénylpipérazine,
(5) la 1-éthyl-4-[3- (2-tolyl) -4-chloro-5-propanesulfonylamino] phénylpipérazine,
(6) la 1-éthyl-4-[3- (2-tolyl)-4-chloro-5-éthanesulfonylamino] phénylpipérazine,
(7) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-butanesulfonylamino] phénylpipérazine,
(8) la 1-méthyl-4-[3-(2-cyanophényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(9) la 1-éthyl-4-[3-(2-cyanophényl)-4-chloro-5-(1-fluoropropyl)] phénylpipérazine,
(10) la 1-méthyl-4- [3-(2-chlorophényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(11) la 1-(2-hydroxyéthyl)-4-[3-(2-chlorophényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(12) la 1-éthyl-4-[3-(2-chlorophényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(13) la 1-méthyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)] phénylpipérazine,
(14) la 1-(2-hydroxyéthyl)-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(15) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)] phénylpipérazine,
(16) la 1-méthyl-4- [3-(2-tolyl)-4-chloro-5-éthanesulfonylamino] phénylpipérazine,
(17) la 1-méthyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylaminol phénylpipérazine,
(18) la 1-méthyl-4- [3-(2-tolyl)-4-chloro-5-butanesulfonylamino] phénylpipérazine,
(19) la 1-éthyl-4- [3-(2-chlorophényl)-4-chloro-5-éthanesulfonylamino]phénylpipérazine,
(20) la 1-éthyl-4-[3-(2-chlorophényl)-4-chloro-5-propanesulfonylamino]phénylpipérazine,
(21) la 1-éthyl-4-[3-(2-chlorophényl)-4-chloro-5-butanesulfonylamino]phénylpipérazine,
(22) la 1-méthyl-4-[3-(2-chlorophényl)-4-chloro-5-éthanesulfonylamino]phénylpipérazine,
(23) la 1-méthyl-4-[3-(2-chlorophényl)-4-chloro-5-propanesulfonylamino]phénylpipérazine,
(24) la 1-méthyl-4-[3-(2-chlorophényl)-4-chloro-5-butanesulfonylamino]phénylpipérazine,
(25) la 1-éthyl-4-[3-(4-fluorophényl)-4-méthoxy-5-éthanesulfonylamino]phénylpipérazine,
(26) la 1-éthyl-4-(3-phényl-4-méthoxy-5-chlorométhyl) phénylpipérazine,
(27) la 1-éthyl-4-{3-phényl-4-méthoxy-5-[1-fluoro-(4-penténYl)]} phénylpipérazine,
(28) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1-fluorobutyl)] phénylpipérazine,
(29) la l-éthyl-4-[3-phényl-4-méthoxy-5-(1-fluoropentyl)] phénylpipérazine,

(30) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluorobutyl)] phénylpipérazine,
(31) la 1-éthyl-4-[3-(2-tolyl)-4-fluoro-5-(1-fluorobutyl)] phénylpipérazine,
(32) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoro-3-méthylbutyl)]phénylpipérazine,
(33) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoroéthyl)] phénylpipérazine,
(34) la 1-méthyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluorobutyl)] phénylpipérazine,
(35) la 1-éthyl-4-[3-(2-chlorophényl)-4-chloro-5-(1-fluorobutyl)]phénylpipérazine,
(36) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(1,1-difluoropropyl)] phénylpipérazine,
(37) la 1-éthyl-4-(3,5-diphényl-4-méthoxy)phénylpipérazine,
(38) la 1-éthyl-4-(3-phényl-4-méthoxy)phénylpipérazine,
(39) la 1-éthyl-4-(3,5-diphényl-4-hydroxy)phénylpipérazine,
(40) la l-éthyl-4-(3-phényl-4-méthoxy-5-propyl)phénylpipérazine,
(41) la 1-éthyl-4-(3,5-diphényl-4-isopropoxy)phénylpipérazine,
(42) la l-éthyl-4-(3-phényl-4-isopropoxy)phénylpipérazine,
(43) la 1-éthyl-4-(3-phényl-4-hydroxy)phénylpipérazine,
(44) la 1-éthyl-4-[2-méthoxy-3-phényl-5- (3-hydroxypropyl)] phénylpipérazine,
(45) la 1-hydroxyéthyl-4-(3,5-diphényl-4-méthoxy) phénylpipérazine
(46) la 1-éthyl-4-[3-(4-fluorophényl)-4-méthoxy-5-propyl] phénylpipérazine,
(47) la 1-éthyl-4- [3-phényl-4-méthoxy-5- (2-hydroxyéthyl)] phénylpipérazine,
(48) la 1-éthyl-4-[2-méthoxy-3-phényl-5-(2-hydroxyéthyl)] phénylpipérazine,
(49) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(3-méthoxypropyl)] phénylpipérazine,
(50) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(3-méthoxyméthoxypropyl)]phénylpipérazine,
(51) la 1-éthyl-4-(3-phényl-4-méthoxy-5-éthyl)phénylpipérazine,
(52) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(3-cyanopropyl)] phénylpipérazine,
(53) la 1-(2-fluoroéthyl)-4-[3-(4-fluorophényl)-4-méthoxy-5-propyl] phénylpipérazine,
(54) la 1-éthyl-4-[3-(4-méthoxyphényl)-4-méthoxy-5-propyl)] phénylpipérazine,
(55) la 1-éthyl-4-(3-phényl-4-méthoxy-5-méthoxycarbonyl) phénylpipérazine,
(56) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(2-hydroxypropyl)] phénylpipérazine,
(57) la 1-éthyl-4- [3-phényl-4-méthoxy-5-(2-fluoroéthyl)] phénylpipérazine,
(58) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(3-fluoropropyl)] phénylpipérazine,
(59) la 1-éthyl-4-[3-(4-fluorophényl)-4-méthoxy-5-isopropyl] phénylpipérazine,
(60) la 1-éthyl-4-[3-(4-fluorophényl)-4-méthoxy-6-isopropyl] phénylpipérazine,
(61) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1-hydroxyisopropyl)] phénylpipérazine,
(62) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1-butoxypropyl)] phénylpipérazine,
(63) la 1-éthyl-4-(3-phényl-4-méthoxy-5-propionyl) phénylpipérazine,
(64) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1-hydroxypropyl)] phénylpipérazine,
(65) la 1-éthyl-4-[3-(2-fluorophényl)-4-méthoxy-5-propyl] phénylpipérazine,
(66) la 1-éthyl-4-[3-(4-trifluorométhylphényl)-4-méthoxy-5-propyl]phénylpipérazine,
(67) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1-fluoroisopropyl)] phénylpipérazine,
(68) la l-éthyl-4-[3-phényl-4-méthoxy-5-(2-hydroxyisopropyl)] phénylpipérazine,
(69) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1-fluoropropyl)] phénylpipérazine,
(70) la 1-éthyl-4-(3-phényl-4-méthoxy-5-cyano)phénylpipérazine,
(71) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(2-furanyl)] phénylpipérazine,
(72) la 1-éthyl-4-[3-(2,4-difluorophényl-4-méthoxy-5-propyl] phénylpipérazine,
(73) la 1-éthyl-4-(3-phényl-4-méthoxy-5-(3-phénylacétyl) phénylpipérazine,
(74) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(4-fluorophényl)acétyl] phénylpipérazine,
(75) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1-hydroxyphénéthyl)] phénylpipérazine,
(76) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(2-tétrahydrofuranyl)] phénylpipérazine,
(77) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1-fluorophénéthyl)] phénylpipérazine,
(78) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(2-pyridyl)] phénylpipérazine,
(79) la 1-éthyl-4-{3-phényl-4-méthoxy-5-[4-fluoro-(1-hydroxyimino)phénéthyl]}phénylpipérazine,
(80) la 1-éthyl-4-{3-phényl-4-méthoxy-5-[1-fluoro-2-(2-pyridyl)éthyl]}phénylpipérazine,
(81) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1-propényl)] phénylpipérazine,
(82) la 1-éthyl-4-[3-(3-fluorophényl)-4-méthoxy-5-propyl] phénylpipérazine,
(83) la l-éthyl-4-(3-phényl-4-méthoxy-5-hydroxyméthyl) phénylpipérazine,
(84) la 1-éthyl-4- [3-phényl-4-méthoxy-5-(4-pyridyl)acétyl] phénylpipérazine,
(85) la 1-éthyl-4-(3-phényl-4-méthoxy-5-méthanesulfinyl) phénylpipérazine,
(86) la 1-éthyl-4-(3-phényl-4-méthoxy-5-éthanesulfinyl) phénylpipérazine,
(87) la 1-éthyl-4-(3-phényl-4-méthoxy-5-formyl)phénylpipérazine,

(88) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1,3-dioxan-2-yl)] phénylpipérazine,
(89) la 1-éthyl-4-(3-phényl-4-méthoxy-5-cyclopropaneacétyl) phénylpipérazine,
(90) la 1-éthyl-4- [3-phényl-4-méthoxy-5-(2-pyridylcarbonyl)] phénylpipérazine,
(91) la 1-éthyl-4-(3-phényl-4-méthoxy-5-amino)phénylpipérazine,
(92) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(2-éthoxycarbonyléthyl)] phénylpipérazine,
(93) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(2-pyridyl) hydroxyméthyl]phénylpipérazine,
(94) la 1-éthyl-4- (3-phényl-5-propyl-6-méthoxy)phénylpipérazine,
(95) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(2-acétyléthyl)] phénylpipérazine,
(96) la 1-éthyl-4-{3-phényl-4-méthoxy-5-[1-(2-pyridylméthoxy)propyl]}phénylpipérazine,
(97) la 1-éthyl-4-[3-(2-tolyl)-4-méthoxy-5-propyl] phénylpipérazine,
(98) la 1-éthyl-4-(3-phényl-4-méthoxy-5-propylamino) phénylpipérazine,
(99) la 1-(3-phényl-4-hydroxy-5-phénylacétyl)phénylpipérazine,
(100) la 1-éthyl-4-(3-phényl-4-méthoxy-5-benzylsulfinyl) phénylpipérazine,
(101) la 1-éthyl-4-(3-phényl-4-méthoxy-5-benzènesulfonylamino) phénylpipérazine,
(102) la 1-éthyl-4-{3-phényl-4-méthoxy-5-[1-fluoro-2-(4-pyridyl)éthyl]}phénylpipérazine,
(103) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(N-éthanesulfonyl-N-méthylamino)]phénylpipérazine,
(104) la 1-éthyl-4-(3-phényl-4-méthoxy-5-éthylaminosulfonyl) phénylpipérazine,
(105) la 1-éthyl-4-(3-phényl-4-méthoxy-5-aminosulfonyl) phénylpipérazine,
(106) la 1-(3-phényl-4-méthoxy-5-phénylacétyl)phénylpipérazine,
(107) la 1-benzyl-4-(3-phényl-4-méthoxy-5-phénylacétyl) phénylpipérazine,
(108) la 1-éthyl-4-[3-phényl-4-chloro-5-(1-fluoropropyl)] phénylpipérazine,
(109) la l-hydroxyéthyl-4-(3-phényl-4-méthoxy-5-phénylacétyl) phénylpipérazine,
(110) la 1-éthyl-4-[3-phényl-5-(1-fluoropropyl)] phénylpipérazine,
(111) la 1-éthyl-4-(3-phényl-5-propionyl)phénylpipérazine,
(112) la 1-éthyl-4- [3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)] phénylpipérazine,
(113) la 1-éthyl-4-[3-(2-méthoxyphényl)-4-méthoxy-5-propyl] phénylpipérazine,
(114) la 1-éthyl-4-(3-phényl-4-méthoxy-5-éthanesulfonyl) phénylpipérazine,
(115) la 1-éthyl-4-(3-phényl-4-méthoxy-5-diméthylaminosulfonyl) phénylpipérazine,
(116) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1-pyrrolidinylsulfonyl)]phénylpipérazine,
(117) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(2,2,2-trifluoroéthyl)sulfonylamino] phénylpipérazine,
(118) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(4-fluorophénylsulfonylamino)]phénylpipérazine,
(119) la 1-éthyl-4-[3-phényl-4-chloro-5-(1-hydroxypropyl)] phénylpipérazine,
(120) la 1-éthyl-4-(3-phényl-4-chloro-5-éthanesulfonyl) phénylpipérazine,
(121) la 1-éthyl-4-(3-phényl-4-chloro-5-propionyl) phénylpipérazine,
(122) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(1-pyrrolidylsulfonyl)]phénylpipérazine,
(123) la 1-éthyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-(1-fluoropropyl)}phénylpipérazine,
(124) la 1-éthyl-4-[3-(2-méthoxyphényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(125) la 1-éthyl-4-[3-(2,4-difluorophényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(126) la 1-éthyl-4-[3-(2-méthoxyméthylphényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(127) la 1-éthyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-cyclopropaneaminosulfonyl}phénylpipérazine,
(128) la 1-éthyl-4-[3-phényl-4-chloro-5-(1-méthylpropyl)] phénylpipérazine,
(129) la 1-éthyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-cyclopropylméthylsulfonyl}phénylpipérazine,
(130) la 1-éthyl-4-(3-phényl-4-fluoro-5-éthanesulfonyl) phénylpipérazine,
(131) la 1-[3-(4-pyridyl)propyl]-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(132) la 1-propyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)] phénylpipérazine,
(133) la 1-éthyl-4-[3-(2-hydroxyméthylphényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(134) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylamino]phénylpipérazine,
(135) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-diméthylaminosulfonyl]phénylpipérazine,
(136) la 1-éthyl-4-[3-(2-tolyl)-4-fluoro-5-méthanesulfonyl] phénylpipérazine,
(137) la 1-éthyl-4-[3-(2-chloro-4-fluorophényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(138) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(1-éthylpropyl)] phénylpipérazine,
(139) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-méthanesulfonyl] phénylpipérazine,
(140) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonyl] phénylpipérazine,
(141) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(1-fluoro-4-penténYl)]phénylpipérazine,
(142) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-propylaminosulfonyl] phénylpipérazine,
(143) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-éthanesulfonylamino] phénylpipérazine,
(144) la 1-éthyl-4-[3-(2-chlorophényl)-4-chloro-5-(2,2,2-trifluoroéthyl)sulfonylamino]phénylpipérazine,
(145) la 1-éthyl-4-[3-(2-tolyl)-4-cyano-5-(1-fluoropropyl)] phénylpipérazine,

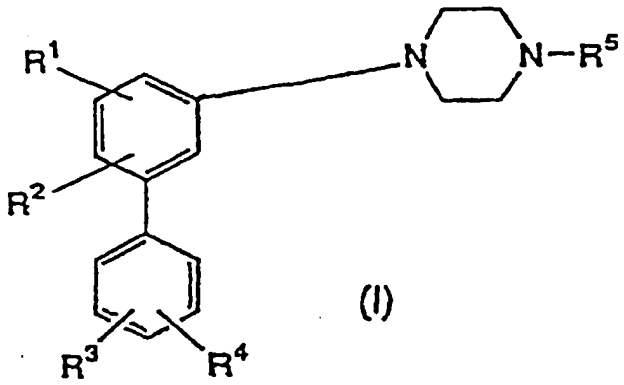
(146) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(3-chloropropyl) sulfonylamino]phénylpipérazine,
(147) la 1-éthyl-4- [3-(2-tolyl)-4-chloro-5-phénylaminosulfonyl] phénylpipérazine,
(148) la 1-éthyl-4- [3-(2-tolyl)-4-chloro-5-benzyloxyméthyl] phénylpipérazine,
(149) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-propoxyméthyl] phénylpipérazine,
(150) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(4-pyridyl) méthoxyméthyl]phénylpipérazine,
(151) la 1-éthyl-4-(3-phényl-4-méthoxy-5-propanesulfonyl) phénylpipérazine,
(152) la 1-éthyl-4-(3-phényl-4-méthoxy-5-butanesulfonyl) phénylpipérazine,
(153) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(2-fluoroéthane) sulfonyl]phénylpipérazine,
(154) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-éthoxyméthyl] phénylpipérazine,
(155) la 1-méthyl-4-[3-(2-tolyl)-4-chloro-5-(1-hydroxybutyl)] phénylpipérazine,
(156) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-allyloxyméthyl] phénylpipérazine,
(157) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-cyclopropylméthoxyméthyl]phénylpipérazine,
(158) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(1-pyrrolidinyl)] phénylpipérazine,
(159) la 1-méthyl-4-[3-(2-chlorophényl)-4-chloro-5-(1-fluorobutyl)]phénylpipérazine,
(160) la 1-méthyl-4-[3-(2-chlorophényl)-4-chloro-5-benzylsulfonylamino]phénylpipérazine,
(161) la 1-méthyl-4-[3-(2-chlorophényl)-4-chloro-5-propanesulfonyl] phénylpipérazine,
(162) la 1-éthyl-4-{3-phényl-4-méthoxy-5-[3-(4-fluorophénoxy)propane]sulfonyl}phénylpipérazine,
(163) la 1-méthyl-4-[3-(2-chlorophényl)-4-chloro-5-isopropylsulfonylamino]phénylpipérazine,
(164) la 1-éthyl-4- [3-phényl-4-méthoxy-5-(2-cyanoéthylsulfonyl)]phénylpipérazine,
(165) la 1-éthyl-4-(3-phényl-4-chloro-5-propanesulfonylamino) phénylpipérazine,
(166) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-difluorométhyl] phénylpipérazine,
(167) la 1-éthyl-4-[3-phényl-4-méthoxy-5-(1,1-difluoropropyl)] phénylpipérazine,
(168) la 1-éthyl-4-[3-(4-méthoxyphényl)-4-chloro-5-propanesulfonylamino]phénylpipérazine,
(169) la 1-méthyl-4-[3-(2-chlorophényl)-4-chloro-5-méthanesulfonylamino]phénylpipérazine,
(170) la 1-éthyl-4-[3-(2,4-dichlorophényl)-4-chloro-5-propanesulfonylamino]phénylpipérazine,
(171) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-(1,3-dithian-2-yl)] phénylpipérazine,
(172) la 1-éthyl-4-[3-phényl-4-chloro-5-propanesulfonyl] phénylpipérazine,
(173) la 1-éthyl-4-[3-(2-tolyl)-4-chloro-5-propanesulfonylaminométhyl]phénylpipérazine,
(174) la 1-méthyl-4-[3-(4-fluorophényl)-4-méthoxy-5-propanesulfonyl]phénylpipérazine,
(175) la 1-éthyl-4-[3-(2-éthylphényl)-4-chloro-5-propanesulfonylamino]phénylpipérazine,
(176) la 1-hydroxyéthyl-4-[3-(4-fluorophényl)-4-méthoxy-5-éthanesulfonyl]phénylpipérazine,
(177) la 1-éthyl-4-[3-(2-formylphényl)-4-chloro-5-propanesulfonylamino]phénylpipérazine,
(178) la 1-éthyl-4-[3-(2-cyanophényl)-4-chloro-5-propanesulfonylamino]phénylpipérazine,
(179) la 1- (2-pyridyléthyl) -4-[3-(4-fluorophényl)-4-méthoxy-5-éthanesulfonyl]phénylpipérazine,
(180) la 1-(2-pyridylméthyl)-4-[3-(4-fluorophényl)-4-méthoxy-5-éthanesulfonyl]phénylpipérazine,
(181) la 1-(3-pyridylméthyl)-4-[3-(4-fluorophényl)-4-méthoxy-5-éthanesulfonyl]phénylpipérazine,
(182) la 1-(4-pyridyléthyl) -4-[3-(4-fluorophényl) -4-méthoxy-5-éthanesulfonyl]phénylpipérazine,
(183) la 1-[3-(4-fluorophényl)-4-méthoxy-5-éthanesulfonyl]phénylpipérazine,
(184) la 1-(2-fluoroéthyl)-4-[3-(4-fluorophényl)-4-méthoxy-5-éthanesulfonyl]phénylpipérazine,
(185) la 1-éthyl-4-[3-(2-chlorophényl)-4-chloro-5-(1-propényl)] phénylpipérazine,
(186) la 1-éthyl-4-[3-(2-chlorophényl)-4-chloro-5-(1-chloropropyl)]phénylpipérazine,
(187) la 1-méthyl-4-[3-phényl-4-chloro-5-(1-fluoropropyl)] phénylpipérazine,
(188) la 1-méthyl-4-[3-(2-hydroxyméthylphényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(189) la 1-éthyl-4-[3-(2-fluorométhylphényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(190) la 1-méthyl-4-{3-(2-fluorométhylphényl)-4-chloro-5-[1-fluoropropyl]}phénylpipérazine,
(191) la 1-éthyl-4-{3-[2-(4-fluorotolyl)]-4-chloro-5-[1-fluoropropyl]}phénylpipérazine,
(192) la 1-[2-(2-pyridyl)éthyl]-4-[3-(2-tolyl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(193) la 1-[2-(2-pyridyl)éthyl]-4-[3-(2-cyanophényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(194) la 1-éthyl-4-[3-(2,6-xylyl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(195) la 1-éthyl-4-{3-(2-trifluorométhylphényl)-4-chloro-5-[1-fluoropropyl]}phénylpipérazine,
(196) la 1-éthyl-4-[3-(2-éthylphényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(197) la 1-(2-hydroxyéthyl)-4-[3-(2-éthylphényl)-4-chloro-5-(1-fluoropropyl)]phénylpipérazine,
(198) la 1-(2-hydroxyéthyl)-4-{3-(2-trifluorométhylphényl)-4-chloro-5-[1-fluoropropyl]}phénylpipérazine,
(199) la 1-méthyl-4-{3-(2-tolyl)-4-chloro-5-[1-fluoropropyl]}phénylpipérazine, et
(200) la 1-(2-hydroxyéthyl)-4-{3-[2-(4-fluorotolyl)]-4-chloro-5 [1-fluoropropyl]}phénylpipérazine.

6. Agent thérapeutique et améliorant destiné à un trouble mental, lequel comprend un dérivé de biphényle ou un sel de celui-ci pharmacologiquement acceptable selon la revendication 1 en tant que principe actif.

7. Agent thérapeutique et améliorant destiné à un trouble mental selon la revendication 6, dans lequel le trouble mental est au moins un trouble choisi parmi le groupe constitué d'un trouble cérébrovasculaire, d'un comportement agressif dû à une démence sénile, d'une excitation mentale, d'une fugue, d'un délire, d'une hallucination, d'une hyperkinésie, d'une schizophrénie, d'un trouble émotionnel, d'une dépression, d'une névrose, d'un trouble psychophysiologique et d'une névrose d'angoisse.

8. Agent thérapeutique et améliorant destiné à des maladies contre lesquelles l'antagonisme au récepteur 2 de la dopamine et/ou l'antagonisme au récepteur 2 de la sérotonine est efficace, comprenant un dérivé de biphényle ou un sel de celui-ci pharmacologiquement acceptable selon la revendication 1 en tant que principe actif.

9. Procédé de préparation d'un dérivé de biphényle représenté par la formule (I) suivante :



(I)

dans laquelle R^1 représente un groupement alkyle en C_1 à C_6 halogéné,

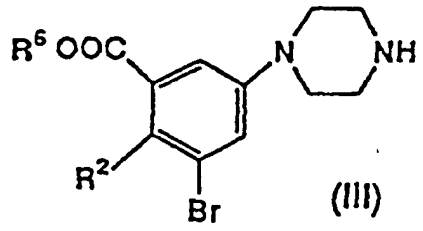
R^2 représente un atome d'hydrogène, un atome d'halogène, un groupement cyano, un groupement hydroxyle, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement alcoxy (en C_1 à C_6) alkyle, un groupement alcoxy en C_1 à C_6 ou un groupement alcoxy en C_1 à C_6 halogéné,

R^3 représente un groupement cyano,

R^4 représente un atome d'hydrogène, un atome d'halogène, un groupement alkyle en C_1 à C_6, un groupement hydroxyalkyle en C_1 à C_6, un groupement hydroxyiminométhyle ou un groupement formyle, et

R^5 représente un groupement hydroxyalkyle en C_1 à C_6,

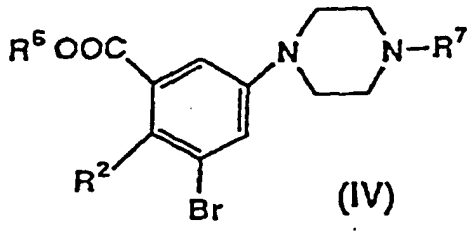
lequel comprend la protection d'un dérivé de phénylpipérazine représenté par la formule (III) suivante :



(III)

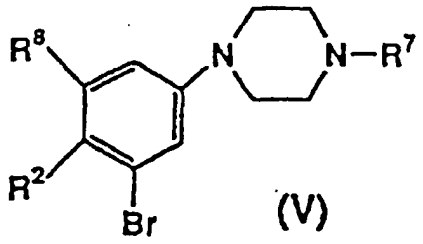
dans laquelle R^2 est tel que défini ci-dessus, et R^6 représente un groupement alkyle en C_1 à C_6,

afin de former un dérivé de phénylpipérazine protégé représenté par la formule (IV) suivante :



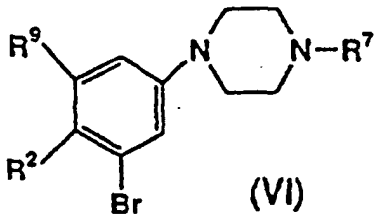
(IV)

dans laquelle R^2 et R^6 sont chacun comme défini ci-dessus, et R^7 représente un groupement amino protecteur, la mise en réaction du dérivé (IV) avec un halogénure d'alkylmagnésium afin de former un dérivé d'hydroxyalkyl-phénylpipérazine représenté par la formule (V) suivante :



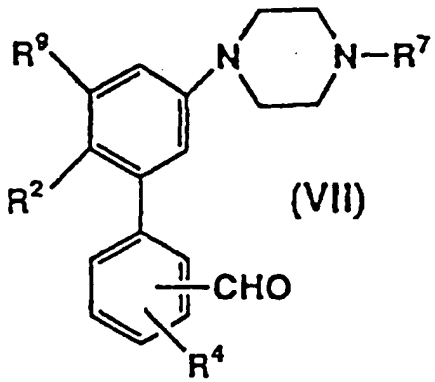
(V)

dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^8 représente un groupement hydroxyalkyle, la mise en réaction du dérivé (V) avec un agent d'halogénation afin de former un dérivé d'alkylphénylpipérazine halogéné représenté par la formule (VI) suivante :



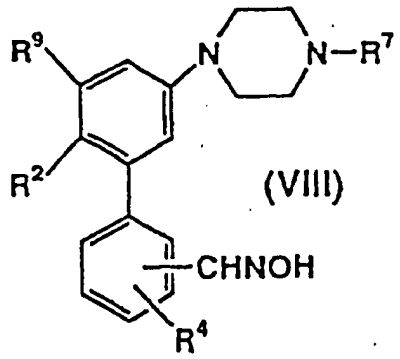
(VI)

dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^9 représente un groupement alkyle halogéné, la mise en réaction du dérivé (VI) avec le 2-(1,3,2-dioxaborinan-2-yl)benzaldéhyde en présence de tétrakis (triphénylphosphine)palladium (0) et de carbonate de césium afin de former un dérivé d'alkylbiphénylpipérazine halogéné protégé représenté par la formule (VII) suivante :

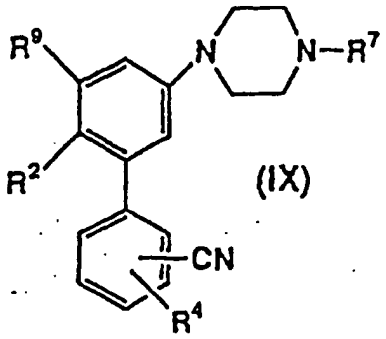


(VII)

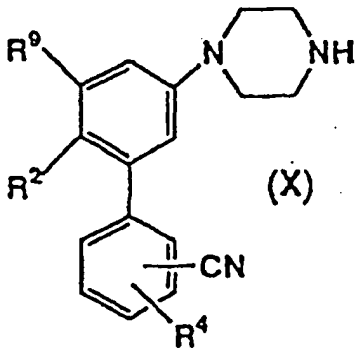
dans laquelle R^2, R^4, R^7 et R^9 sont chacun comme défini ci-dessus,
la mise en réaction du dérivé (VII) avec de l'hydroxylamine afin de former un dérivé d'oxime d'alkylbiphénylpipérazine halogéné protégé représenté par la formule (VIII) suivante :



dans laquelle R^2, R^4, R^7 et R^9 sont chacun comme défini ci-dessus,
la mise en réaction du dérivé (VIII) avec de l'anhydride acétique en présence de pyridine et de 4-diméthylaminopyridine afin de former un dérivé d'alkylcyanobiphénylpipérazine halogéné protégé représenté par la formule (IX) suivante :



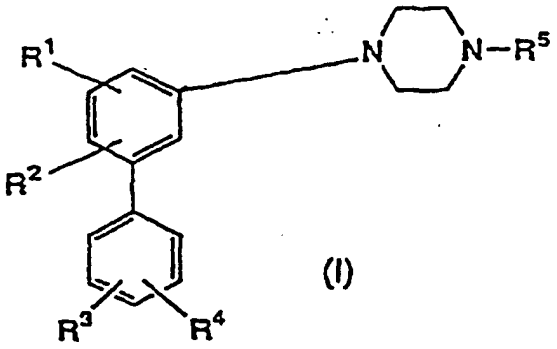
dans laquelle R^2, R^4, R^7 et R^9 sont chacun comme défini ci-dessus, le traitement du dérivé (IX) avec un acide afin de former un dérivé d'alkylcyanobiphénylpipérazine halogéné représenté par la formule (X) suivante :



dans laquelle R^2, R^4 et R^9 sont chacun comme défini ci-dessus,
et la mise en réaction du dérivé (X) avec un alcanol halogéné.

10. Procédé selon la revendication 9, dans lequel l'agent d'halogénation est le trifluorure de diéthylaminosoufre.

11. Procédé de préparation d'un dérivé de biphényle représenté par la formule (I) suivante :



(I)

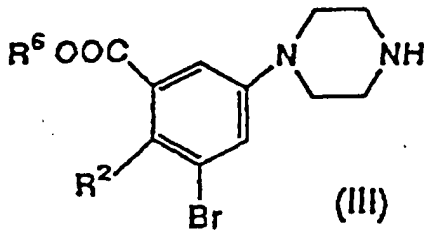
dans laquelle R^1 représente un groupement alkylsulfonylamino en C_1 à C_6,

R^2 représente un atome d'halogène,

R^3 et R^4 peuvent être identiques ou différents l'un de l'autre et chacun représente un groupement alkyle en C_1 à C_6,

R^5 représente un atome d'hydrogène, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement hydroxyalkyle en C_1 à C_6, un groupement hétéroarylalkyle, un groupement aralkyle, un groupement alcoxy (en C_1 à C_6) carbonyle ou un groupement aryloxycarbonyle,

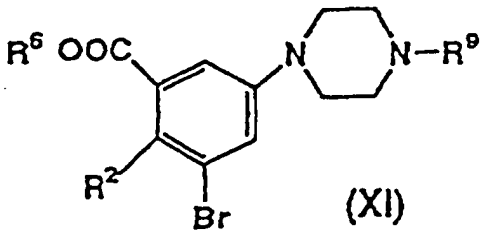
lequel comprend la mise en réaction d'un dérivé de phénylpipérazine représenté par la formule (III) suivante :



(III)

dans laquelle R^2 est comme défini ci-dessus, et R^6 représente un groupement alkyle en C_1 à C_6,

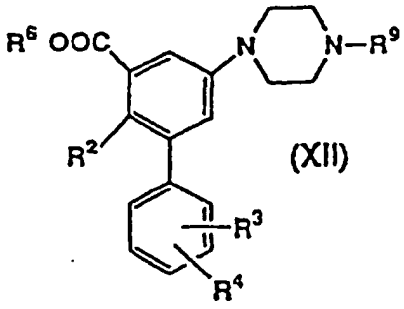
avec un halogénure d'alkyle afin de former un dérivé de phénylalkylpipérazine représenté par la formule (XI) suivante :



(XI)

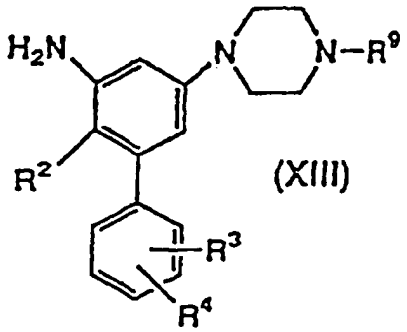
dans laquelle R^2 et R^6 sont chacun comme défini ci-dessus et R^9 représente un groupement alkyle halogéné,

la mise en réaction du dérivé (XI) avec de l'acide tolylborique en présence d'acétate de palladium afin de former un dérivé de biphénylalkylpipérazine représenté par la formule (XII) suivante :



(XII)

dans laquelle R^2, R^3, R^4, R^6 et R^9 sont chacun comme défini ci-dessus,
l'hydrolyse du dérivé (XII), la mise en réaction du produit de l'hydrolyse avec du chlorocarbonate d'éthyle en présence d'une base, la mise en réaction du produit de cette réaction avec de l'azoture de sodium et une base, successivement, afin de former un dérivé d'aminobiphénylalkylpipérazine représenté par la formule (XIII) suivante :

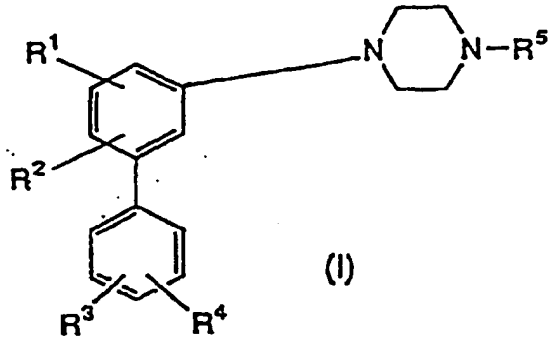


(XIII)

dans laquelle R^2, R^3, R^4 et R^9 sont chacun comme défini ci-dessus, et la mise en réaction du dérivé (XIII) avec un halogénure d'alkylsulfonyle,
où l'expression groupement hétéroaryle indique un groupement thiényle, un groupement furanyle, un groupement pyranyle, un groupement imidazolyle, un groupement thiazolyle, un groupement pyridyle ou un groupement pyrazyle, l'expression groupement hétéroarylalkyle indique un groupement thiénylméthyle, un groupement furfuryle, un groupement imidazolylméthyle, un groupement thiazolylméthyle, un groupement pyridylméthyle ou un groupement pyrazylméthyle, et l'expression groupement hétéroarylalkyle halogéné indique un groupement hétéroarylalkyle comme défini ci-dessus dans lequel au moins un atome d'hydrogène est remplacé par un atome d'halogène et où l'expression groupement aryle indique un groupement aryle non substitué, un groupement tolyle, un groupement xylyle, un groupement méthoxyphényle, un groupement chlorophényle, un groupement bromophényle, un groupement fluorophényle, un groupement nitrophényle ou un groupement cyanophényle.

12. Procédé selon la revendication 11, dans lequel la base utilisée dans la réaction du produit de l'hydrolyse avec du chlorocarbonate d'éthyle est la triéthylamine.

13. Procédé de préparation d'un dérivé de biphényle représenté par la formule (I) suivante



(I)

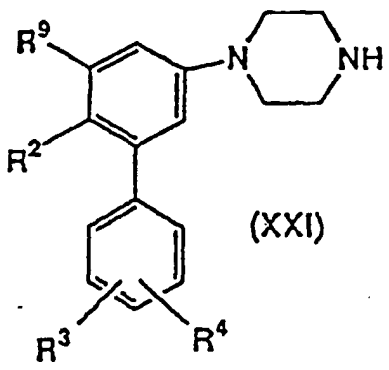
dans laquelle R^1 représente un atome d'hydrogène, un atome d'halogène, un groupement hydroxyle, un groupement amino, un groupement cyano, un groupement pyrrolidyle, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement cyanoalkyle en C_1 à C_6, un groupement hydroxyalkyle en C_1 à C_6, un groupement aminoalkyle en C_1 à C_6, un groupement cycloalkyle, un groupement cycloalkylalkyle, un groupement alcoxy (en C_1 à C_6) alkyle, un groupement hétéroarylalkyle, un groupement hétéroarylalkyle halogéné, un groupement acylalkyle en C_1 à C_6, un groupement hétéroarylalcoxyalkyle, un groupement cycloalkyloxyalkyle, un groupement aralkyloxyalkyle, un groupement alcényloxyalkyle, un groupement alcoxy (en C_1 à C_6) carbonylalkyle, un groupement alcoxy (en C_1 à C_6) alcoxyalkyle, un groupement arylhydroxyalkyle, un groupement hydroxyhétéroarylalkyle, un groupement cycloalkylalcoxyalkyle, un groupement alcényle, un groupement alcényle halogéné, un groupement alcynyle, un groupement aralkyle, un groupement aralkyle halogéné, un groupement hydroxyaralkyle, un groupement hydroxyiminoaralkyle halogéné, un groupement alcoxy en C_1 à C_6, un groupement alcoxy en C_1 à C_6 halogéné, un groupement alcoxy (en C_1 à C_6) alcoxy, un groupement aryle, un groupement hydroxyaryle, un groupement aryle halogéné, un groupement alcoxy (en C_1 à C_6) aryle, un groupement hétéroaryle, un groupement hydroxyhétéroaryle, un groupement hétéroaryle halogéné, un groupement alcoxy (en C_1 à C_6) hétéroaryle, un groupement formyle, un groupement acyle en C_1 à C_6, un groupement acyle aromatique, un groupement acyle hétéroaromatique, un groupement aralkylcarbonyle, un groupement cycloalkylalkylcarbonyle, un groupement hétéroarylalkylcarbonyle, un groupement aralkylcarbonyle halogéné, un groupement alcoxy (en C_1 à C_6) carbonyle, un groupement aryloxycarbonyle, un groupement alkylamino en C_1 à C_6, un groupement alkylsulfonylamino en C_1 à C_6, un groupement alkylsulfonylamino en C_1 à C_6 halogéné, un groupement arylsulfonylamino, un groupement arylsulfonylamino halogéné, un groupement aralkylsulfonylamino, un groupement cycloéther, un groupement acétal cyclique en C_1 à C_6, un groupement thioacétal cyclique en C_1 à C_6, un groupement alkylsulfinyle en C_1 à C_6, un groupement arylsulfinyle, un groupement aralkylsulfinyle, un groupement hétéroarylsulfinyle, un groupement alkylsulfonyle en C_1 à C_6, un groupement arylsulfonyle, un groupement aralkylsulfonyle, un groupement hétéroarylsulfonyle, un groupement cycloalkylsulfonyle, un groupement aminosulfonyle, un groupement alkylaminosulfonyle en C_1 à C_6, un groupement arylaminosulfonyle, un groupement pyrrolidylsulfonyle, un groupement cycloalkylaminosulfonyle, un groupement alkylsulfonyle en C_1 à C_6 halogéné, un groupement aryloxyalkyl (en C_1 à C_6) sulfonyle halogéné ou un groupement cyanoalkyl (en C_1 à C_6) sulfonyle,

R^2 et R^3 peuvent être identiques ou différents l'un de l'autre et chacun représente un atome d'hydrogène, un atome d'halogène, un groupement cyano, un groupement hydroxyle, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement alcoxyalkyle en C_1 à C_6, un groupement alcoxy en C_1 à C_6 ou un groupement alcoxy en C_1 à C_6 halogéné,

R^4 représente un atome d'hydrogène, un atome d'halogène, un groupement alkyle en C_1 à C_6, un groupement hydroxyalkyle en C_1 à C_6, un groupement hydroxyiminométhyle ou un groupement formyle,

R^5 représente un atome d'hydrogène, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement hydroxyalkyle en C_1 à C_6, un groupement hétéroarylalkyle, un groupement aralkyle, un groupement alcoxy (en C_1 à C_6) carbonyle ou un groupement aryloxycarbonyle,

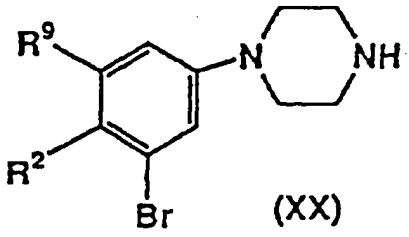
lequel comprend la mise en réaction d'un dérivé de biphénylpipérazine représenté par la formule (XXI) suivante :



(XXI)

dans laquelle R^2, R^3 et R^4 sont chacun comme défini ci-dessus et R^9 représente un groupement alkyle halogéné, avec un dérivé actif représenté par la formule : R^5L (dans laquelle R^5 est comme défini ci-dessus, et L représente un groupe partant),
où l'expression groupement hétéroaryle indique un groupement thiényle, un groupement furanyle, un groupement pyranyle, un groupement imidazolyle, un groupement thiazolyle, un groupement pyridyle ou un groupement pyrazyle, l'expression groupement hétéroarylalkyle indique un groupement thiénylméthyle, un groupement furfuryle, un groupement imidazolylméthyle, un groupement thiazolylméthyle, un groupement pyridylméthyle ou un groupement pyrazylméthyle, et l'expression groupement hétéroarylalkyle halogéné indique un groupement hétéroarylalkyle comme défini ci-dessus dans lequel au moins un atome d'hydrogène est remplacé par un atome d'halogène, et où l'expression groupement aryle indique un groupement aryle non substitué, un groupement tolyle, un groupement xylyle, un groupement méthoxyphényle, un groupement chlorophényle, un groupement bromophényle, un groupement fluorophényle, un groupement nitrophényle ou un groupement cyanophényle.

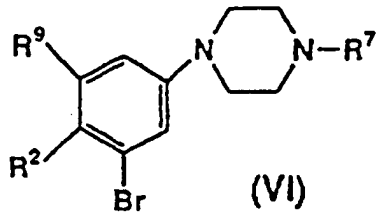
14. Procédé selon la revendication 13, lequel comprend en outre la mise en réaction d'un dérivé d'alkylphénylpipérazine halogéné représenté par la formule (XX) suivante :



(XX)

dans laquelle R^2 est comme défini ci-dessus et R^9 représente un groupement alkyle halogéné,
avec un dérivé de 2-(1,3,2-dioxaborinan-2-yl)benzène ou un dérivé de l'acide phénylborique en présence de triphénylphosphinepalladium et de phosphate de tripotassium afin de former un dérivé de biphénylpipérazine représenté par la formule (XXI) ci-dessus.

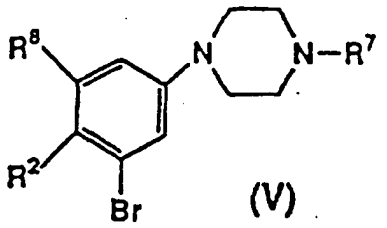
15. Procédé selon la revendication 14, lequel comprend en outre la déprotection d'un dérivé d'alkylphénylpipérazine halogéné protégé représenté par la formule (VI) suivante :



(VI)

dans laquelle R^2 et R^9 sont chacun comme défini ci-dessus, et R^7 représente un groupement amino protecteur, afin de former un dérivé d'alkylphénylpipérazine halogéné représenté par la formule (XX) ci-dessus.

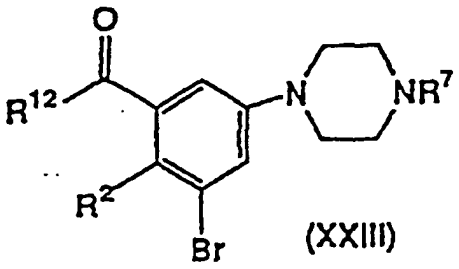
16. Procédé selon la revendication 15, lequel comprend en outre la mise en réaction d'un dérivé d'hydroxyalkylphénylpipérazine protégé représenté par la formule (V) suivante :



(V)

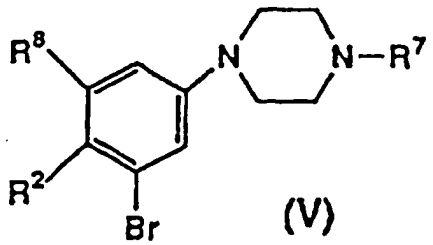
dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^8 représente un groupement hydroxyalkyle, avec un agent d'halogénation afin de former un dérivé d'alkylphénylpipérazine halogéné protégé représenté par la formule (VI) ci-dessus.

17. Procédé selon la revendication 15, lequel comprend en outre la réduction d'un dérivé d'acylphénylpipérazine protégé représenté par la formule (XXIII) suivante :



(XXIII)

dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^{12} représente un groupement alkyle en C_1 à C_6, en un dérivé d'hydroxyalkylphénylpipérazine protégé représenté par la formule (V) suivante :

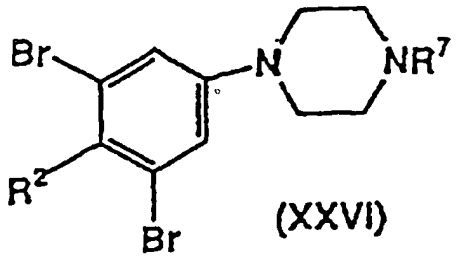


(V)

dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^8 représente un groupement hydroxyalkyle,

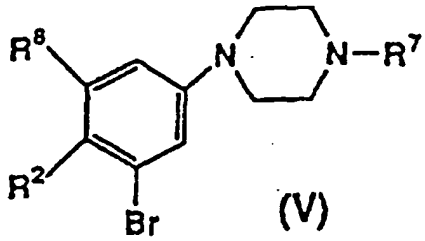
et la mise en réaction du dérivé (V) avec un agent d'halogénation afin de former un dérivé d'alkylphénylpipérazine halogéné représenté par la formule (VI) ci-dessus.

18. Procédé selon la revendication 15, lequel comprend en outre la mise en réaction d'un dérivé de dibromophénylpipérazine protégé représenté par la formule (XXVI) suivante :



(XXVI)

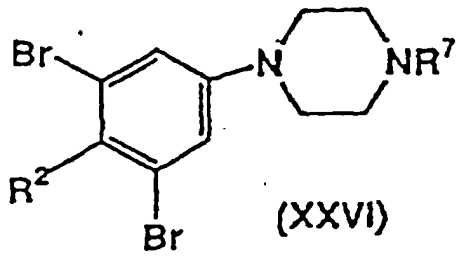
dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus,
avec un aldéhyde aliphatique en C_1 à C_6 en présence d'une base afin de former un dérivé d'hydroxyalkylphénylpipérazine protégé représenté par la formule (V) suivante :



(V)

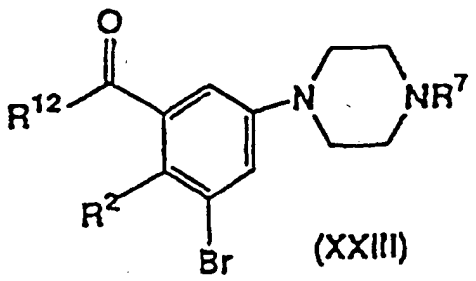
dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^8 représente un groupement hydroxyalkyle, et la mise en réaction du dérivé (V) avec un agent d'halogénation afin de former un dérivé d'alkylphénylpipérazine halogéné représenté par la formule (VI) ci-dessus.

19. Procédé selon la revendication 15, lequel comprend en outre la mise en réaction d'un dérivé de dibromophénylpipérazine protégé représenté par la formule (XXVI) suivante :



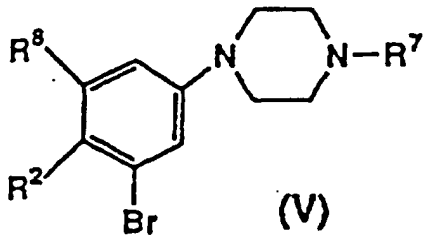
(XXVI)

dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus,
avec un anhydride d'acide en présence d'une base afin de former un dérivé d'acylphénylpipérazine protégé représenté par la formule (XXIII) suivante :



(XXIII)

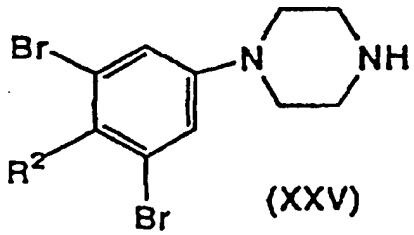
dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^{12} représente un groupement alkyle en C_1 à C_6, la réduction du dérivé (XXIII) en un dérivé d'hydroxyalkylphénylpipérazine protégé représenté par la formule (V) suivante :



(V)

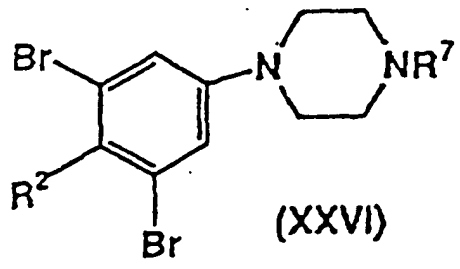
dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^8 représente un groupement hydroxyalkyle, et la mise en réaction du dérivé (V) avec un agent d'halogénation afin de former un dérivé d'alkylphénylpipérazine halogéné représenté par la formule (VI) ci-dessus.

20. Procédé selon la revendication 15, lequel comprend en outre la protection d'un dérivé de dibromophénylpipérazine représenté par la formule (XXV) suivante :



(XXV)

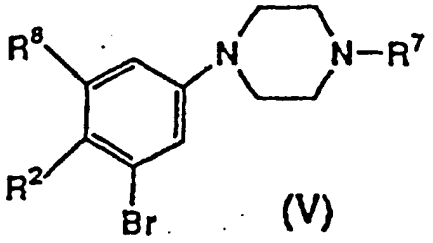
dans laquelle R^2 est comme défini ci-dessus,
afin de former un dérivé de dibromophénylpipérazine protégé représenté par la formule (XXVI) suivante :



(XXVI)

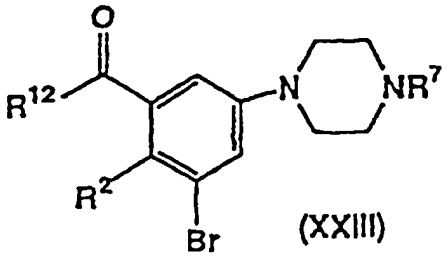
dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus,
la conversion du dérivé (XXVI) en un dérivé d'hydroxyalkylphénylpipérazine protégé représenté par la formule (V)

suivante :



(V)

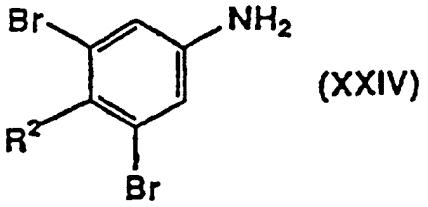
dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^8 représente un groupement hydroxyalkyle, soit en faisant réagir le dérivé (XXVI) avec un aldéhyde aliphatique en C_1 à C_6 en présence d'une base, soit en faisant réagir le dérivé (XXVI) avec un anhydride d'acide en présence d'une base afin de former un dérivé d'acyl-phénylpipérazine protégé représenté par la formule (XXIII) suivante :



(XXIII)

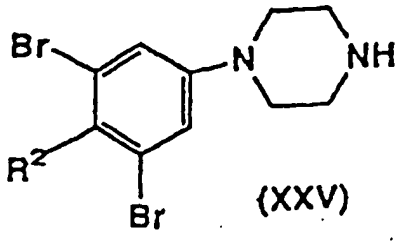
dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^{12} représente un groupement alkyle en C_1 à C_6, et la réduction du dérivé (XXIII), ainsi que la mise en réaction du dérivé (V) avec un agent d'halogénation afin de former un dérivé d'alkylphénylpipérazine halogéné protégé représenté par la formule (VI) ci-dessus.

21. Procédé selon la revendication 15, lequel comprend en outre la mise en réaction d'un dérivé de dibromoaniline représenté par la formule (XXIV) suivante :



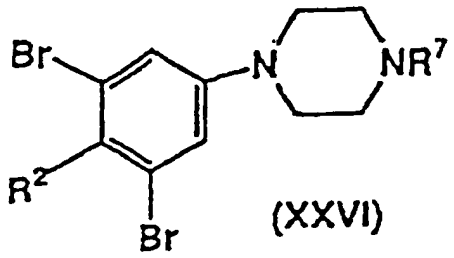
(XXIV)

dans laquelle R^2 est comme défini ci-dessus,
avec de la bis(2-chloro-éthyl)amine afin de former un dérivé de dibromophénylpipérazine représenté par la formule (XXV) suivante :



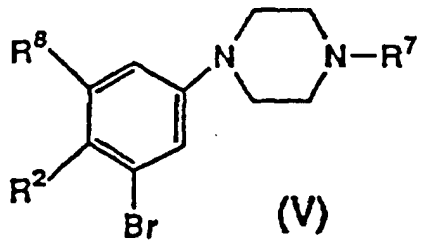
(XXV)

dans laquelle R^2 est comme défini ci-dessus,
la protection du dérivé ((XXV) afin de former un dérivé d dibromophénylpipérazine protégé représenté par la formule (XXVI suivante :



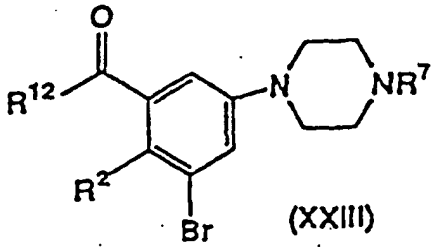
(XXVI)

dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus,
la conversion du dérivé (XXVI) en un dérivé d'hydroxyalkylphénylpipérazine protégé représenté par la formule (V) suivante :



(V)

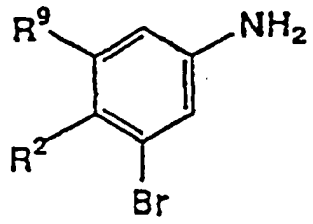
dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^8 représente un groupement hydroxyalkyle, soit en faisant réagir le dérivé (XXVI) avec un aldéhyde aliphatique en C_1 à C_6 en présence d'une base, soit en faisant réagir le dérivé (XXVI) avec un anhydride d'acide en présence d'une base afin de former un dérivé d'acylphénylpipérazine protégé représenté par la formule (XXIII) suivante :



(XXIII)

dans laquelle R^2 et R^7 sont chacun comme défini ci-dessus, et R^{12} représente un groupement alkyle en C_1 à C_6, et la réduction du dérivé (XXIII) ainsi que la mise en réaction du dérivé (V) avec un agent d'halogénation afin de former un dérivé d'alkylphénylpipérazine halogéné protégé représenté par la formule (VI) ci-dessus.

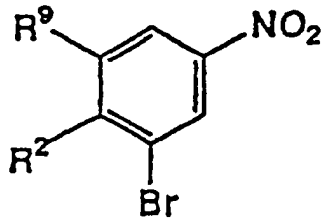
22. Procédé selon la revendication 14, lequel comprend en outre la mise en réaction d'un dérivé d'alkylaniline halogéné représenté par la formule (XIX) suivante :



(XIX)

dans laquelle R^2 et R^9 sont chacun comme défini ci-dessus,
avec de la bis(2-chloro-éthyl)amine afin de former un dérivé d'alkylphénylpipérazine halogéné représenté par la formule (XX) ci-dessus.

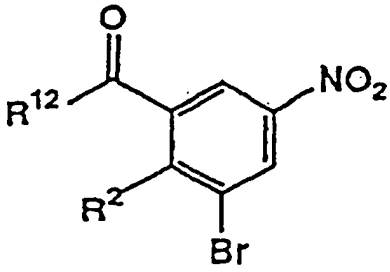
23. Procédé selon la revendication 22, lequel comprend en outre la réduction d'un dérivé d'alkylnitrobenzène halogéné représenté par la formule (XVIII) suivante :



(XVIII)

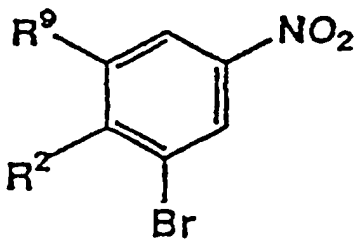
dans laquelle R^2 et R^9 sont chacun comme défini ci-dessus,
en un dérivé d'alkylaniline halogéné représenté par la formule (XIX) ci-dessus.

24. Procédé selon la revendication 22, lequel comprend en outre la réduction d'un dérivé d'acylnitrobenzène représenté par la formule (XVII) suivante :



(XVII)

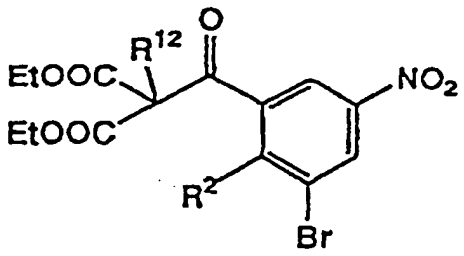
dans laquelle R^2 est comme défini ci-dessus et R^{12} représente un groupement alkyle en C_1 à C_6,
la mise en réaction du produit de la réduction avec un agent d'halogénation afin de former un dérivé d'alkylnitrobenzène halogéné représenté par la formule (XVIII) suivante :



(XVIII)

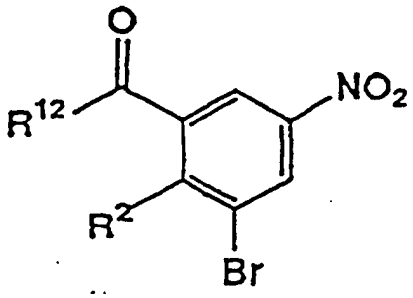
dans laquelle R^2 et R^9 sont chacun comme défini ci-dessus,
et la réduction du dérivé (XVIII) en un dérivé d'alkylaniline halogéné représenté par la formule (XIX) ci-dessus.

25. Procédé selon la revendication 22, lequel comprend en outre la mise en réaction d'un dérivé d'ester d'acide malonique représenté par la formule (XVI) suivante :



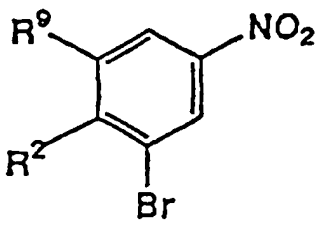
(XVI)

dans laquelle R^2 est comme défini ci-dessus et R^{12} représente un groupement alkyle en C_1 à C_6,
avec un acide ou une base afin de former un dérivé d'acylnitrobenzène représenté par la formule (XVII) suivante :



(XVII)

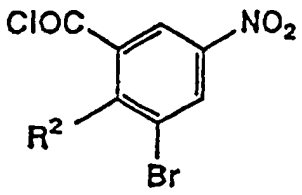
dans laquelle R^2 et R^{12} sont chacun comme défini ci-dessus,
la réduction du dérivé (XVII), la mise en réaction du produit de la réduction avec un agent d'halogénation afin de former un dérivé d'alkylnitrobenzène halogéné représenté par la formule (XVIII) suivante :



(XVIII)

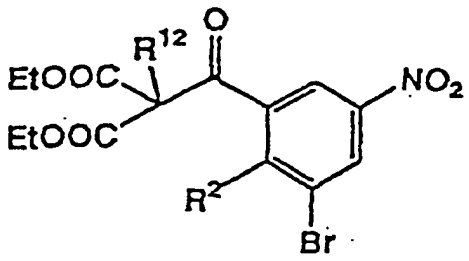
dans laquelle R^2 et R^9 sont chacun comme défini ci-dessus,
et la réduction du dérivé (XVIII) en un dérivé d'alkylaniline halogéné représenté par la formule (XIX) ci-dessus.

26. Procédé selon la revendication 22, lequel comprend en outre la mise en réaction d'un dérivé de chlorure de nitrobenzoyle représenté par la formule (XV) suivante :



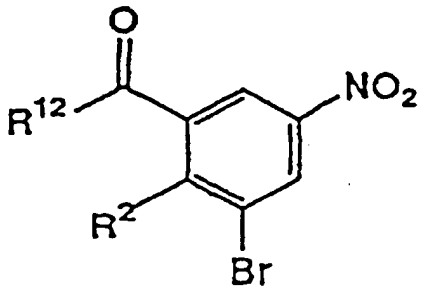
(XV)

dans laquelle R^2 est comme défini ci-dessus,
avec un ester d'acide alkylmalonique en présence d'une base afin de former un dérivé d'ester d'acide malonique représenté par la formule (XVI) suivante :



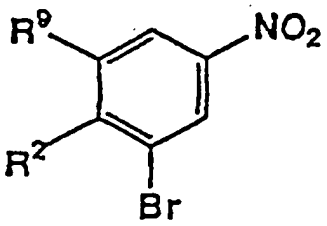
(XVI)

dans laquelle R^2 est comme défini ci-dessus et R^{12} représente un groupement alkyle en C_1 à C_6,
la mise en réaction du dérivé (XVI) avec un acide ou une base afin de former un dérivé d'acylnitrobenzène représenté par la formule (XVII) suivante :



(XVII)

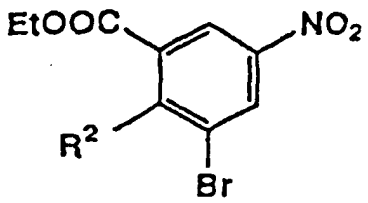
dans laquelle R^2 et R^{12} sont chacun comme défini ci-dessus,
la réduction du dérivé (XVII), la mise en réaction du produit de la réduction avec un agent d'halogénation afin de former un dérivé d'alkylnitrobenzène halogéné représenté par la formule (XVIII) suivante :



(XVIII)

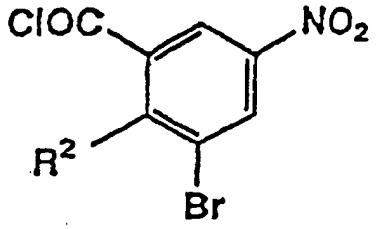
dans laquelle R^2 et R^9 sont chacun comme défini ci-dessus,
et la réduction du dérivé (XVIII) en un dérivé d'alkylaniline halogéné représenté par la formule (XIX) ci-dessus.

27. Procédé selon la revendication 22, lequel comprend en outre l'hydrolyse d'un dérivé d'ester d'acide nitrobenzoique représenté par la formule (XIV) suivante :



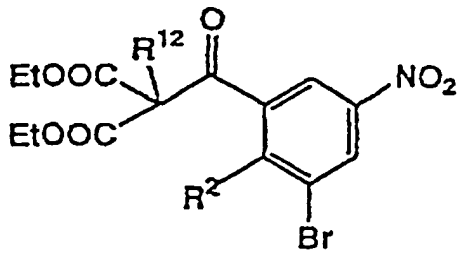
(XIV)

dans laquelle R^2 est comme défini ci-dessus,
la mise en réaction du produit de l'hydrolyse avec un agent de chloration afin de former un dérivé de chlorure de nitrobenzoyle représenté par la formule (XV) suivante :



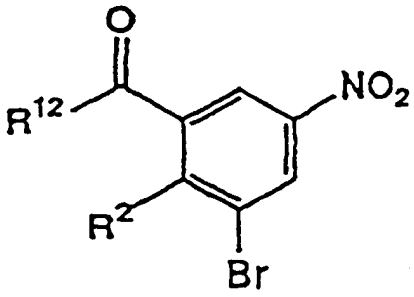
(XV)

dans laquelle R^2 est comme défini ci-dessus,
la mise en réaction du dérivé (XV) avec un ester d'acide alkylmalonique en présence d'une base afin de former un dérivé d'ester d'acide malonique représenté par la formule (XVI) suivante :



(XVI)

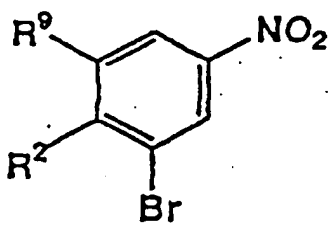
dans laquelle R^2 est comme défini ci-dessus et R^{12} représente un groupement alkyle en C_1 à C_6,
la mise en réaction du dérivé (XVI) avec un acide ou une base afin de former un dérivé d'acylnitrobenzène représenté par la formule (XVII) suivante :



(XVII)

dans laquelle R^2 et R^{12} sont chacun comme défini ci-dessus,
la réduction du dérivé (XVII), la mise en réaction du produit de la réduction avec un agent d'halogénation afin de

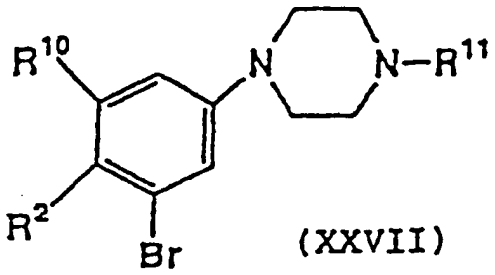
former un dérivé d'alkylnitrobenzène halogéné représenté par la formule (XVIII) suivante :



(XVIII)

dans laquelle R^2 et R^9 sont chacun comme défini ci-dessus,
et la réduction du dérivé (XVIII) en un dérivé d'alkylaniline halogéné représenté par la formule (XIX) ci-dessus.

28. Dérivé de phénylpipérazine représenté par la formule générale (XXVII) suivante ou sel de celui-ci :



(XXVII)

où R^2 représente un atome d'hydrogène, un atome d'halogène, un groupement cyano, un groupement hydroxyle, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement alcoxy en C_1 à C_6 ou un groupement alcoxy en C_1 à C_6 halogéné, R^{10} représente un groupement alkyle en C_1 à C_6 halogéné, un groupement hydroxyalkyle en C_1 à C_6, un atome d'halogène, un groupement alkylsulfonyle en C_1 à C_6, un groupement alcoxy (en C_1 à C_6) carbonyle, un groupement carboxyle, un groupement alcényle, un groupement (pyridylthio)carbonyle ou un groupement acyle en C_1 à C_6, et R^{11} représente un atome d'hydrogène, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement hydroxyalkyle en C_1 à C_6, un groupement tri(alkyl en C_1 à C_6) silyloxyalkyle en C_1 à C_6, un groupement hétéroarylalkyle, un groupement aralkyle, un groupement alcoxy (en C_1 à C_6) carbonyle, un groupement aryloxycarbonyle ou un groupement amino protecteur,
où l'expression groupement hétéroaryle indique un groupement thiényle, un groupement furanyle, un groupement pyranyle, un groupement imidazolyle, un groupement thiazolyle, un groupement pyridyle ou un groupement pyrazyle, l'expression groupement hétéroarylalkyle indique un groupement thiénylméthyle, un groupement furfuryle, un groupement imidazolylméthyle, un groupement thiazolylméthyle, un groupement pyridylméthyle ou un groupement pyrazylméthyle, et l'expression groupement hétéroarylalkyle halogéné indique un groupement hétéroarylalkyle comme défini ci-dessus dans lequel au moins un atome d'hydrogène est remplacé par un atome d'halogène, et où l'expression groupement aryle indique un groupement aryle non substitué, un groupement tolyle, un groupement xylyle, un groupement méthoxyphényle, un groupement chlorophényle, un groupement bromophényle, un groupement fluorophényle, un groupement nitrophényle ou un groupement cyanophényle.

29. Dérivé de phénylpipérazine ou sel de celui-ci selon la revendication 28, dans lequel R^2 est comme défini ci-dessus, R^{10} représente un groupement alkyle en C_1 à C_6 halogéné ou un groupement hydroxyalkyle en C_1 à C_6, et R^{11} représente un atome d'hydrogène, un groupement hydroxyalkyle en C_1 à C_6 ou un groupement amino protecteur.

30. Dérivé de phénylpipérazine ou sel de celui-ci selon la revendication 29, dans lequel R^2 représente un atome d'hydrogène, un atome d'halogène, un groupement alkyle en C_1 à C_6, un groupement alkyle en C_1 à C_6 halogéné, un groupement alcoxy en C_1 à C_6, un groupement alcoxy en C_1 à C_6 halogéné ou un groupement cyano, et R^{10} et R^{11} sont chacun comme défini ci-dessus.

31. Composition pharmacologique qui comprend une quantité efficace au niveau thérapeutique ou améliorant d'un

dérivé de biphényle ou d'un sel de celui-ci pharmacologiquement acceptable selon la revendication 1 et un excipient pharmacologiquement acceptable.

32. Utilisation d'un dérivé de biphényle ou d'un sel de celui-ci pharmacologiquement acceptable selon la revendication 1 pour la fabrication d'un médicament destiné à traiter ou à améliorer une maladie contre laquelle l'antagonisme au récepteur 2 de la dopamine et/ou l'antagonisme au récepteur 2 de la sérotonine est efficace.